

METHODS OF TREATING INFLAMMATORY CONDITIONS**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of priority of US Provisional Application No. 63/426,620, filed November 18, 2022; US Provisional Application No. 63/447,436, filed February 22, 2023; and US Provisional Application No. 63/463,742, filed May 3, 2023, each of which is incorporated by reference herein in its entirety for any purpose.

FIELD

[0002] The present disclosure relates generally to compounds, compositions, and methods for treating diseases, such as peripheral and/or systemic inflammatory conditions.

BACKGROUND

[0003] Hepatocyte growth factor (HGF) is a pleiotropic protein factor involved in numerous biological processes including embryonic and organ development, regeneration, and inflammation. HGF is a key contributor to cortical, motor, sensory, sympathetic, and parasympathetic neuronal development and maturation. HGF is translated and secreted as inactive pro-HGF, but following cleavage, the resultant α and β -subunits are joined by a disulfide linkage to form the active heterodimer. Expression of HGF predominantly occurs in mesenchymal cells such as fibroblasts, chondroblasts, adipocytes, and the endothelium. Expression has also been demonstrated in the central nervous system (CNS) including neurons, astrocytes, and ependymal cells (Nakamura and Mizuno, 2010).

[0004] All biological activities of HGF are mediated through MET, a transmembrane receptor tyrosine kinase that serves as the sole known receptor for HGF. MET has known involvement in a variety of biological processes, with demonstrated roles in development, regeneration, and response to injury. Upon binding of HGF to the extracellular domain of MET, homo-dimerization of the MET protein leads to auto-phosphorylation of the intracellular domain. Phosphorylation of MET intracellular domains leads to recruitment and phosphorylation of a variety of effector proteins including Gab1, GRB2, Phospholipase C, and Stat3 (Gherardi et al., 2012; Organ and Tsao, 2011). These effector proteins then interact with downstream signaling pathways, including PI3K/Akt, Ras/Raf/MAPK, RAC1/CDC42, and RAP/FAK among others, to influence an array of cellular components including gene regulation, cytoskeletal rearrangements, cell cycle progression, cell adhesion, survival, and proliferation (Organ and Tsao, 2011).

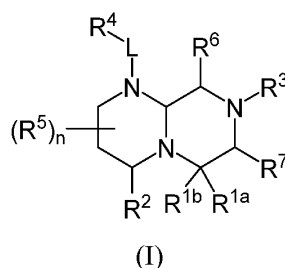
[0005] HGF is a key regulator of inflammation and autoimmunity. HGF activity reduces the expression of the pro-inflammatory cytokine IL-6 and promotes expression of the anti-inflammatory IL-10 in monocytes (Molnarfi et al., 2015). Additionally, HGF increases tolerogenic dendritic cells and attenuates cytotoxic T-cell activity (Ilangumaran et al., 2016). These effects of HGF activity on inflammation and immune function would likely be beneficial in inflammatory conditions.

[0006] Although progress has been made in this field, there remains a need for improved compounds and methods for treatment of peripheral and/or systemic inflammatory conditions.

SUMMARY

[0007] Provided herein are compounds that modulate HGF for use in treating peripheral and/or systemic inflammatory conditions. Nonlimiting exemplary embodiments include:

1. A method of treating a peripheral and/or systemic inflammatory condition in a subject in need thereof, comprising administering an effective amount of a compound of Formula (I):



or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, wherein:

L is a direct bond, $-C(=O)-$, $-(CR^aR^b)_m-C(=O)-$, $-C(=O)-(CR^aR^b)_m-$, or $-(CR^aR^b)_m-$;

each R^a and R^b is independently H, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;

R^{1a} and R^{1b} are independently H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halo, or C₆-C₁₀ arylalkyl;

R^2 is H, oxo, or thioxo;

R^3 is C₂-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₁₂ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₆-C₁₀ arylalkyl, 5- to 10-membered heteroarylalkyl, or 5- to 10-membered heterocyclylalkyl, wherein the 5- to 10-membered heteroarylalkyl or 5- to 10-membered heterocyclylalkyl contains 1-3 heteroatoms selected from nitrogen and oxygen;

R^4 is C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, or 5- to 10-membered heterocyclyl, wherein the 5- to 10-membered heteroaryl or 5- to 10-membered heterocyclyl contains 1-3 heteroatoms selected from nitrogen and oxygen;

each R^5 is independently C₁-C₆ alkyl, oxo, or halo;

R^6 is H, C₁-C₆ alkyl, or oxo;

R^7 is H or oxo;

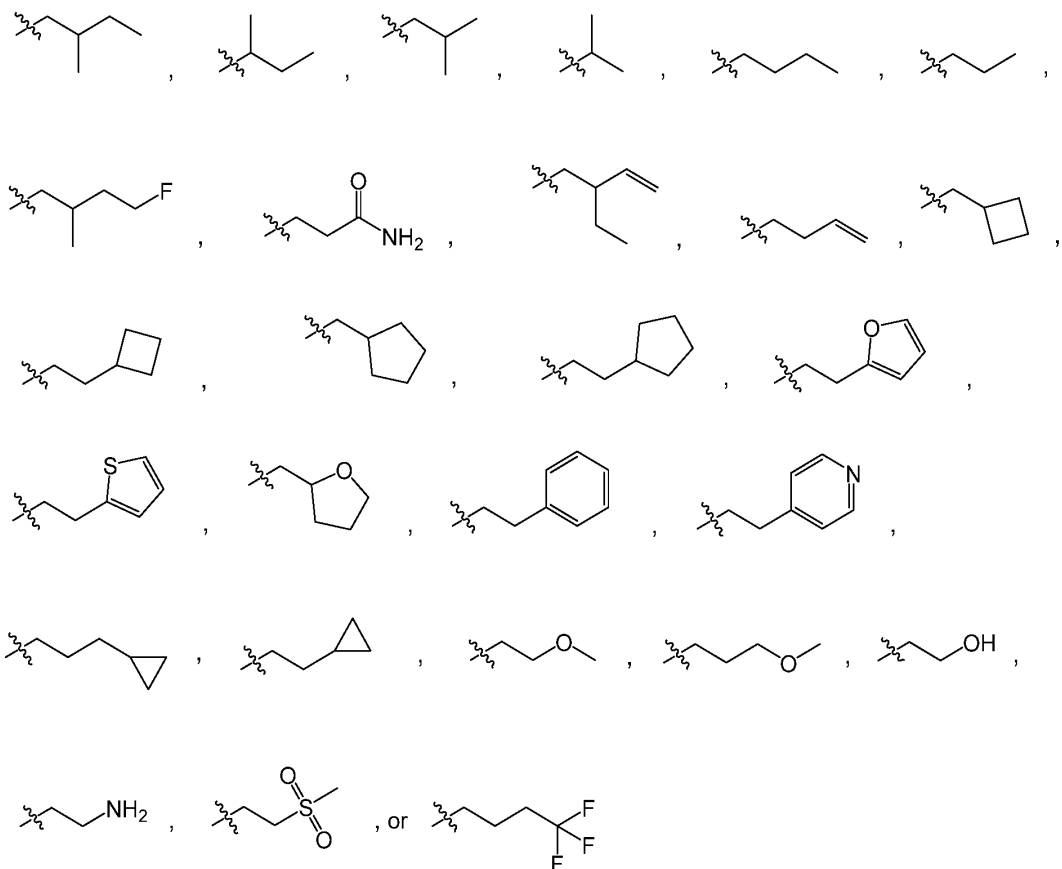
m is 1 or 2; and

n is an integer from 0 to 3;

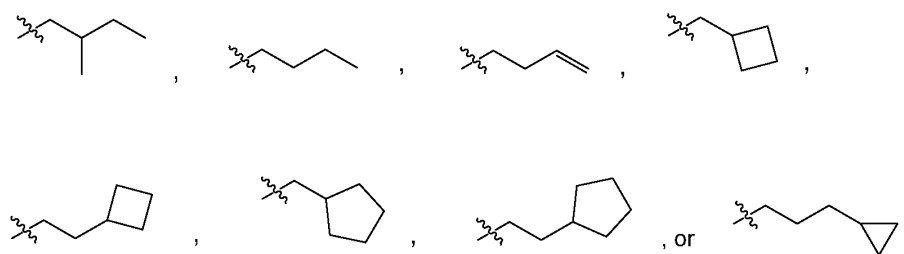
wherein each C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkylalkyl, C₆-C₁₀ aryl, C₆-C₁₀ arylalkyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroarylalkyl, 5- to 10-membered heterocyclyl, and 5- to 10-membered heterocyclylalkyl is optionally substituted with one to five substituents selected from hydroxyl, halo, amino, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, cyano, -(C=O)NH₂, nitro, -SO₂(C₁-C₆ alkyl), and -CO₂H.

2. The method of embodiment 1, wherein L is -C(=O)- or -(CR^aR^b)_m-.
3. The method of embodiment 1 or 2, wherein L is a -C(=O)-.
4. The method of embodiment 1 or 2, wherein L is -(CR^aR^b)_m-.
5. The method of embodiment 4, wherein R^a and R^b are each H, and m is 1.
6. The method of any one of embodiments 1-5, wherein R^{1a} and R^{1b} are each independently H; C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from halo, -CO₂H, and -C(=O)NH₂; C₁-C₆ alkoxy; halo; or C₆-C₁₀ arylalkyl optionally substituted by 1-3 substituents selected from halo and amino.
7. The method of embodiment 6, wherein R^{1a} and R^{1b} are each independently H, methyl, fluoro, 2-methylbutyl, -CH₂F, methoxy, -CH₂CO₂H, -CH₂C(=O)NH₂, benzyl, or 4-aminobenzyl.
8. The method of embodiment 6, wherein R^{1a} and R^{1b} are each independently H or C₁-C₃ alkyl.
9. The method of embodiment 8, wherein R^{1a} is methyl and R^{1b} is H.

10. The method of embodiment 8, wherein R^{1a} and R^{1b} are each H.
11. The method of any one of embodiments 1-10, wherein R^2 is H.
12. The method of any one of embodiments 1-10, wherein R^2 is thioxo.
13. The method of any one of embodiments 1-10, wherein R^2 is oxo.
14. The method of any one of embodiments 1-13, wherein R^3 is C₃-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₁₂ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₆-C₁₀ arylalkyl, 5- to 10-membered heteroarylalkyl, or 5- to 10-membered heterocyclalkyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, or heterocyclalkyl is optionally substituted with one to five substituents selected from hydroxyl, halo, amino, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, cyano, $-(C=O)NH_2$, nitro, $-SO_2(C_1-C_6 \text{ alkyl})$, and $-CO_2H$.
15. The method of any one of embodiments 1-13, wherein R^3 is C₂-C₆ alkyl optionally substituted by 1-3 substituents selected from halo, C₁-C₃ alkoxy, hydroxy, $-NH_2$, $-SO_2(C_1-C_3 \text{ alkyl})$, and $-C(=O)NH_2$; C₂-C₆ alkenyl; C₃-C₆ cycloalkylalkyl; 5- to 6-membered heteroarylalkyl; 5- to 6-membered heterocyclalkyl; or C₆ arylalkyl.
16. The method of embodiment 15, wherein R^3 is C₂ alkyl substituted by 1-3 substituents selected from C₁-C₃ alkoxy, hydroxy, $-NH_2$, and $-SO_2(C_1-C_3 \text{ alkyl})$.
17. The method of any one of embodiments 14-16, wherein R^3 is:



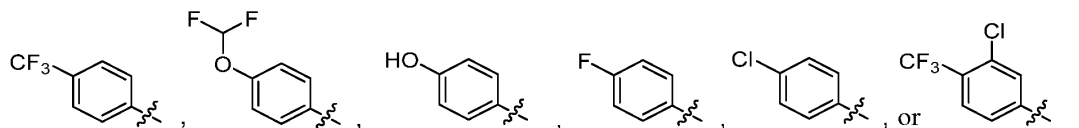
18. The method of embodiment 17, wherein R^3 is:



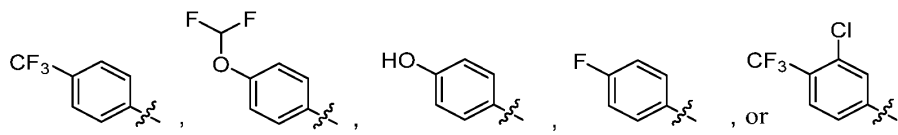
19. The method of any one of embodiments 1-18, wherein R^4 is C_6 - C_{10} aryl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1 - C_6 haloalkyl, and C_1 - C_6 haloalkoxy.

20. The method of embodiment 19, wherein R^4 is phenyl substituted with 1-3 substituents selected from $-CF_3$, $-OCHF_2$, $-OH$, fluoro, and chloro.

21. The method of embodiment 20, wherein R^4 is:



22. The method of embodiment 21, wherein R^4 is:

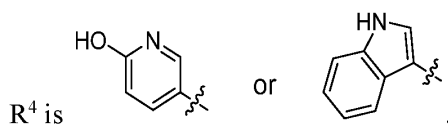


23. The method of any one of embodiments 1-18, wherein R^4 is 5- to 10-membered heteroaryl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1 - C_6 haloalkyl, and C_1 - C_6 haloalkoxy.

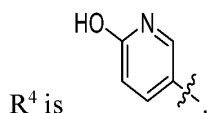
24. The method of embodiment 23, wherein

R^4 is pyridyl or indolyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1 - C_6 haloalkyl, and C_1 - C_6 haloalkoxy.

25. The method of embodiment 24, wherein

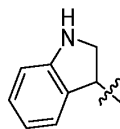


26. The method of embodiment 25, wherein



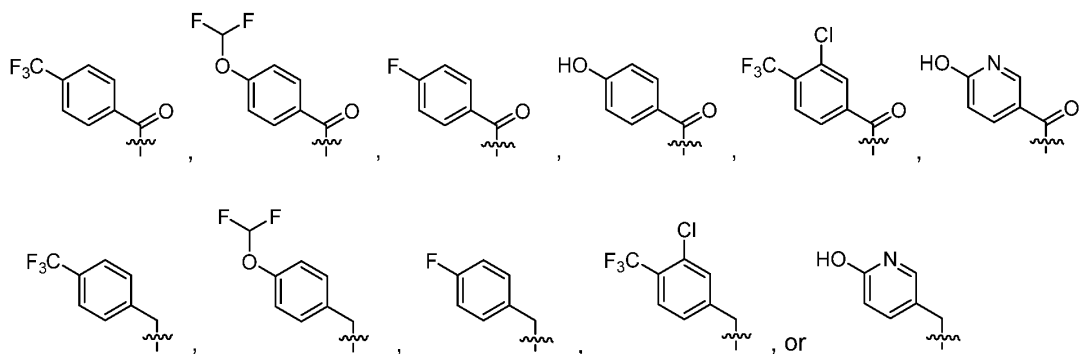
27. The method of any one of embodiments 1-18, wherein R^4 is 5- to 10-membered heterocyclyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1 - C_6 haloalkyl, and C_1 - C_6 haloalkoxy.

28. The method of embodiment 27, wherein R^4 is indoliny.



29. The method of embodiment 28, wherein R^4 is

30. The method of any one of embodiments 1-26, wherein $-L-R^4$ is:



31. The method of any one of embodiments 1-30, wherein n is 0.

32. The method of any one of embodiments 1-30, wherein n is 1.

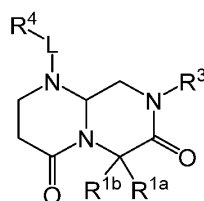
33. The method of embodiment 32, wherein R^5 is oxo or halo.

34. The method of embodiment 33, wherein R^5 is oxo or fluoro.

35. The method of any one of embodiments 1-34, wherein R^6 is H.

36. The method of any one of embodiments 1-35, wherein R^7 is oxo.

37. The method of any one of embodiments 1-10, 13-31, 35, and 36, wherein the compound is of Formula (V):



(V), or a pharmaceutically acceptable

salt, isotopic form, or stereoisomer thereof.

38. The method of embodiment 37, wherein:

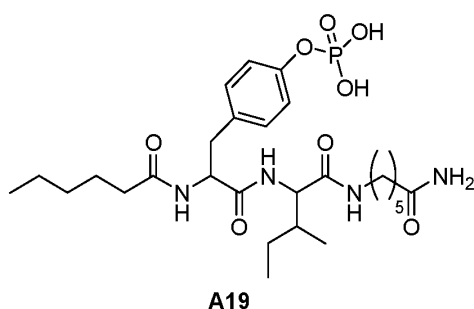
L is -C(=O)- or -CH₂-;

R^{1a} and R^{1b} are independently H or C₁-C₃ alkyl optionally substituted with -CO₂H;

R³ is C₄-C₅ alkyl, C₄-C₅ alkenyl, or C₁-C₃ alkyl substituted with C₃-C₅ cycloalkyl; and

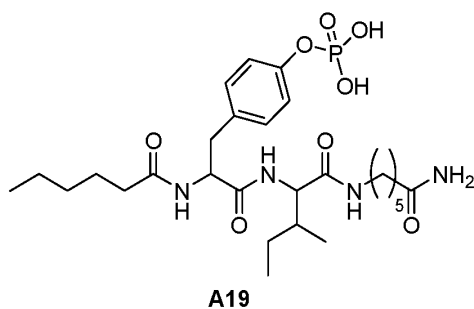
R⁴ is phenyl or pyridyl substituted with 1-3 substituents selected from -CF₃, -OCHF₂, -OH, fluoro, and chloro.

39. A method of treating a peripheral and/or systemic inflammatory condition in a subject in need thereof, comprising administering an effective amount of Compound A19:



or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

40. A method of treating a peripheral and/or systemic inflammatory condition in a subject in need thereof, comprising administering an effective amount of a compound selected from the compounds of Table 1A and Compound A19:



and pharmaceutically acceptable salts, isotopic forms, or stereoisomers thereof.

41. The method of any one of the preceding embodiments, wherein the peripheral and/or systemic inflammatory condition is inflammatory bowel disease, Crohn's disease, ulcerative colitis, coeliac disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus,

dermatomyositis, polymyositis, noninfectious uveitis, optic neuritis, Leber hereditary optic neuropathy (LHON), macular degeneration, retinal degeneration, myasthenia gravis, type 2 diabetes, obesity, coronary heart disease, gout, fatty liver disease, seasonal allergies, chronic obstructive pulmonary disease (COPD), or endometriosis.

42. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is inflammatory bowel disease.

43. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is Crohn's disease.

44. The method of embodiment 43, wherein the peripheral and/or systemic inflammatory condition is ulcerative colitis.

45. The method of embodiment 43, wherein the peripheral and/or systemic inflammatory condition is coeliac disease.

46. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is rheumatoid arthritis.

47. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is psoriasis.

48. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is noninfectious uveitis.

49. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is type 2 diabetes.

50. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is obesity.

51. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is coronary heart disease.

52. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is gout.

53. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is fatty liver disease.
54. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is seasonal allergies.
55. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is COPD.
56. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is endometriosis.
57. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is systemic lupus erythematosus.
58. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is dermatomyositis.
59. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is polymyositis.
60. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is opticus neuritis.
61. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is LHON.
62. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is macular degeneration.
63. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is retinal degeneration.
64. The method of any one of embodiments 1-41, wherein the peripheral and/or systemic inflammatory condition is myasthenia gravis.
65. The method of any one of embodiments 1-64, wherein the compound reduces inflammation associated with the inflammatory condition.

66. The method of any one of embodiments 1-65, wherein the compound reduces hypoxia associated with the inflammation.
67. The method of any one of the preceding embodiments, wherein the compound reduces pain associated with the inflammatory condition.
68. The method of any one of the preceding embodiments, wherein the compound decreases the level in the subject of at least one proinflammatory molecule.
69. The method of embodiment 68, wherein the compound decreases the level of at least one proinflammatory molecule selected G-CSF, CCL3, CXCL1, CXCL2, CXCL10, IL-1 α , IL-1 β , IL-4, IL-10, IL-12p70, IL-17A, TNF α , and IFN γ .
70. The method of any one of the preceding embodiments, wherein the compound decreases the level of at least one proinflammatory molecule selected from IL-1 β , IL-4, IL-6, TNF- α , and IFN γ .
71. The method of any one of embodiments 1-70, wherein the peripheral and/or systemic inflammatory condition is not caused by neuroinflammation or a disease or disorder of the central nervous system.
72. The method of any one of embodiments 1-71, wherein the peripheral and/or systemic inflammatory condition is not caused by Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, traumatic brain injury, or sensorineural hearing and vision loss.
73. The method of any one of embodiments 1-70, wherein the peripheral and/or systemic inflammatory condition is not associated with neuroinflammation or a disease or disorder of the central nervous system.
74. The method of any one of embodiments 1-73, wherein the peripheral and/or systemic inflammatory condition is not associated with Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, traumatic brain injury, or sensorineural hearing and vision loss.
75. The method of any one of embodiments 1-74, wherein the subject is not suffering from Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, traumatic brain injury, sensorineural hearing and vision loss, or a disease or disorder of the central nervous system.

76. The method of any one of the preceding embodiments, wherein the compound is formulated in a pharmaceutical composition.

DETAILED DESCRIPTION

Definitions

[0008] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the disclosure. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. To the extent any material incorporated herein by reference is inconsistent with the express content of this disclosure, the express content controls. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

[0009] Unless the context requires otherwise, throughout the present specification and claims, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.”

[0010] In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. Also, any number range recited herein relating to any physical feature, such as polymer subunits, size, or thickness, are to be understood to include any integer within the recited range, unless otherwise indicated. As used herein, the terms “about” and “approximately” mean $\pm 20\%$, $\pm 10\%$, $\pm 5\%$, or $\pm 1\%$ of the indicated range, value, or structure, unless otherwise indicated.

[0011] Reference throughout this specification to “one embodiment” or “an embodiment” means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment of the present disclosure. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” in various places

throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0012] “Amino” refers to the -NH_2 radical.

[0013] “Carboxy” or “carboxyl” refers to the $\text{-CO}_2\text{H}$ radical.

[0014] “Cyano” refers to the -CN radical.

[0015] “Hydroxy” or “hydroxyl” refers to the -OH radical.

[0016] “Nitro” refers to the -NO_2 radical.

[0017] “Oxo” refers to the =O substituent.

[0018] “Thioxo” refers to the =S substituent.

[0019] “Thiol” refers to the -SH substituent.

[0020] “Alkyl” refers to an unbranched or branched saturated hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, having from one to twelve carbon atoms ($\text{C}_1\text{-C}_{12}$ alkyl), preferably one to eight carbon atoms ($\text{C}_1\text{-C}_8$ alkyl), one to six carbon atoms ($\text{C}_1\text{-C}_6$ alkyl), or one to three carbon atoms ($\text{C}_1\text{-C}_3$ alkyl) and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl and the like. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted.

[0021] “Alkenyl” refers to an unbranched or branched unsaturated hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which contains one or more carbon-carbon double bonds, having from two to twelve carbon atoms ($\text{C}_2\text{-C}_{12}$ alkenyl), preferably two to eight carbon atoms ($\text{C}_2\text{-C}_8$ alkenyl) or two to six carbon atoms ($\text{C}_2\text{-C}_6$ alkenyl), and which is attached to the rest of the molecule by a single bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted.

[0022] “Alkynyl” refers to an unbranched or branched unsaturated hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which contains one or more carbon-carbon triple bonds, having from two to twelve carbon atoms ($\text{C}_2\text{-C}_{12}$ alkynyl), preferably two to eight carbon atoms ($\text{C}_2\text{-C}_8$ alkynyl) or two to six carbon atoms ($\text{C}_2\text{-C}_6$ alkynyl), and which is attached to the rest of the molecule by a single bond, *e.g.*, ethynyl, propynyl, butynyl, pentynyl,

hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted.

[0023] “Alkoxy” refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above containing one to twelve carbon atoms. Preferred alkoxy groups have one to six carbon atoms (*i.e.*, C_1 - C_6 alkoxy) or one to three carbon atoms (*i.e.*, C_1 - C_3 alkoxy) in the alkyl radical. Unless stated otherwise specifically in the specification, an alkoxy group is optionally substituted.

[0024] “Aromatic ring” refers to a cyclic planar portion of a molecule (*i.e.*, a radical) with a ring of resonance bonds that exhibits increased stability relative to other connective arrangements with the same sets of atoms. Generally, aromatic rings contain a set of covalently bound co-planar atoms and comprise a number of π -electrons (for example, alternating double and single bonds) that is even but not a multiple of 4 (*i.e.*, $4n + 2$ π -electrons, where $n = 0, 1, 2, 3$, etc.). Aromatic rings include, but are not limited to, phenyl, naphthenyl, imidazolyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridonyl, pyridazinyl, pyrimidonyl. Unless stated otherwise specifically in the specification, an aromatic ring includes all radicals that are optionally substituted.

[0025] “Aryl” refers to a carbocyclic ring system radical comprising 6 to 18 carbon atoms and at least one aromatic ring (*i.e.*, C_6 - C_{18} aryl), preferably having 6 to 10 carbon atoms (*i.e.*, C_6 - C_{10} aryl). For purposes of embodiments of this disclosure, the aryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, phenyl, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl group is optionally substituted.

[0026] “Arylalkyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene chain and R_c is one or more aryl radicals as defined above, for example, benzyl, diphenylmethyl and the like. An arylalkyl group may contain a C_1 - C_{10} alkylene chain connected to a C_6 - C_{10} aryl radical (*i.e.*, C_6 - C_{10} arylalkyl). Unless stated otherwise specifically in the specification, an arylalkyl group is optionally substituted.

[0027] “Cycloalkyl” refers to a stable non-aromatic monocyclic or polycyclic carbocyclic radical consisting solely of carbon and hydrogen atoms, which may include fused or bridged

ring systems, having from three to fifteen carbon atoms (*i.e.*, C₃-C₁₅ cycloalkyl), preferably having from three to ten carbon atoms (*i.e.*, C₃-C₁₀ cycloalkyl) or three to six carbon atoms (*i.e.*, C₃-C₆ cycloalkyl), and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyl also includes “spiro cycloalkyl” when there are two positions for substitution on the same carbon atom. Polycyclic radicals include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group is optionally substituted.

[0028] “Cycloalkylalkyl” refers to a radical of the formula -R_b-R_c where R_b is an alkylene chain and R_c is one or more cycloalkyl radicals as defined above, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and the like. A cycloalkylalkyl group may contain a C₁-C₁₀ alkylene chain connected to a C₃-C₁₂ cycloalkyl radical (*i.e.*, C₃-C₁₂ cycloalkylalkyl) or a C₁-C₁₀ alkylene chain connected to a C₃-C₆ cycloalkyl radical (*i.e.*, C₃-C₆ cycloalkylalkyl). Unless stated otherwise specifically in the specification, a cycloalkylalkyl group is optionally substituted.

[0029] “Fused” refers to any ring structure described herein which is fused to an existing ring structure in the compounds of the disclosure. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring is replaced with a nitrogen atom.

[0030] “Halo” or “halogen” refers to bromo, chloro, fluoro, or iodo.

[0031] “Haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. A preferred haloalkyl group includes an alkyl group having one to six carbon atoms and that is substituted by one or more halo radicals (*i.e.*, C₁-C₆ haloalkyl). The halo radicals may be all the same or the halo radicals may be different. Unless stated otherwise specifically in the specification, a haloalkyl group is optionally substituted.

[0032] “Haloalkoxy” refers to a radical of the formula -OR_a where R_a is a haloalkyl radical as defined herein containing one to twelve carbon atoms. A preferred haloalkoxy group includes an alkoxy group having one to six carbon atoms (*i.e.*, C₁-C₆ haloalkoxy) or having one to three carbon atoms (C₁-C₃ haloalkoxy) and that is substituted by one or more halo radicals.

The halo radicals may all be the same or the halo radicals may all be different. Unless stated otherwise specifically in the specification, a haloalkoxy group is optionally substituted.

[0033] “Heteroaryl” refers to an aromatic group (e.g., a 5-14 membered ring system) having a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 1 to 10 ring carbon atoms and 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur within the ring. Preferred heteroaryl groups have a 5- to 10-membered ring system containing one to four heteroatoms selected from nitrogen, oxygen, and sulfur (*i.e.*, a 5- to 10-membered heteroaryl) and a 5- to 6-membered ring system containing one to four heteroatoms selected from nitrogen, oxygen, and sulfur (*i.e.*, a 5- to 6-membered heteroaryl). For purposes of embodiments of this disclosure, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused or bridged ring systems. Examples of heteroaryl groups include pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (*i.e.*, thienyl). A heteroaryl may comprise one or more N-oxide (N-O-) moieties, such as pyridine-N-oxide. Unless stated otherwise specifically in the specification, a heteroaryl group is optionally substituted.

[0034] “Heteroarylalkyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene chain and R_c is one or more heteroaryl radicals as defined above. A heteroarylalkyl group may contain a C₁-C₁₀ alkylene chain connected to a 5- to 10-membered heteroaryl group (*i.e.*, 5- to 10-membered heteroarylalkyl) or a C₁-C₁₀ alkylene chain connected to a 5- to 6-membered heteroaryl group (*i.e.*, 5- to 6-membered heteroarylalkyl). Unless stated otherwise specifically in the specification, a heteroarylalkyl group is optionally substituted.

[0035] “Heterocyclyl” refers to a saturated or unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term “heterocyclyl” includes heterocycloalkenyl groups (*i.e.*, the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged or spiro, and may comprise one or more oxo (C=O) or N-oxide (N-O-) moieties. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (*i.e.*, can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring

containing at least one heteroatom, which ring may be fused to an aryl or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 1 to 10 ring carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms, and 1 to 5 ring heteroatoms, 1 to 4 heteroatoms, 1 to 3 heteroatoms, or 1 to 2 heteroatoms independently selected from nitrogen, sulfur, and oxygen. Preferred heterocyclyls have five to 10 members in the ring system including one to four heteroatoms selected from nitrogen and oxygen (*i.e.*, 5- to 10-membered heterocyclyl) or five to eight members in the ring system including one to four heteroatoms selected from nitrogen and oxygen (*i.e.*, 5- to 8-membered heterocyclyl). Examples of heterocyclyl groups include dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranlyl, thiomorpholyl, thiamorpholyl, 1-oxo-thiomorpholyl and 1,1-dioxo-thiomorpholyl. Unless stated otherwise specifically in the specification, a heterocyclyl group is optionally substituted.

[0036] “Heterocyclylalkyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene chain and R_c is one or more heterocyclyl radicals as defined above. A heterocyclylalkyl group may contain a C_1 - C_{10} alkylene chain connected to a 5- to 10-membered heterocyclyl radical (*i.e.*, 5- to 10-membered heterocyclylalkyl) or a C_1 - C_{10} alkylene chain connected to a 5- to 8-membered heterocyclyl radical (*i.e.*, 5- to 8-membered heterocyclylalkyl). Unless stated otherwise specifically in the specification, a heterocyclylalkyl group is optionally substituted.

[0037] In some embodiments, the term “substituted” as used herein means any of the above groups, or other substituents (*e.g.*, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{12} cycloalkyl, C_3 - C_{12} cycloalkylalkyl, aryl, and heteroaryl) wherein at least one hydrogen atom (*e.g.*, 1, 2, 3, or all hydrogen atoms) is replaced by a bond to a non-hydrogen atom such as, but not limited to: a halogen atom such as F, Cl, Br, and I (*i.e.*, “halo”); an oxygen atom in groups such as hydroxyl groups or alkoxy groups (*e.g.*, alkoxy or haloalkoxy); a nitrogen atom in groups such as amines (*e.g.*, $-NH_2$), amides (*e.g.*, $-(C=O)NH_2$), and nitro; alkyl groups including one or more halogen, such as F, Cl, Br, and I (*e.g.*, haloalkyl); and cyano.

[0038] It is understood that each choice for L, R^{1a} , R^{1b} , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 is optionally substituted as described above unless specifically stated otherwise, and provided that all valences are satisfied by the substitution. Specifically, each choice for L, R^{1a} , R^{1b} , R^2 , R^3 ,

R⁴, R⁵, R⁶, and R⁷ is optionally substituted unless specifically stated otherwise, and provided such substitution results in a stable molecule (*e.g.*, groups such as H and halo are not optionally substituted).

[0039] “Peripheral inflammation” and “systemic inflammation” refer to the activation of the innate or adaptive immune system and the release of inflammatory cytokine signaling molecules in response to various pathological stimuli outside of the central nervous system. Tissues that generate or respond to peripheral inflammatory signaling include muscle and connective tissue, the gastrointestinal tract and enteric nervous system, thoracic organs, blood, skin, and lymphatic tissue.

[0040] “Effective amount” or “therapeutically effective amount” of a compound or a composition refers to that amount of the compound or the composition that results in an intended result as desired based on the disclosure herein. Effective amounts can be determined by standard pharmaceutical procedures in cell cultures or experimental animals including, without limitation, by determining the ED₅₀ (the dose therapeutically effective in 50% of the population) and the LD₅₀ (the dose lethal to 50% of the population). In some embodiments, an effective amount of a compound results in reduction or inhibition of symptoms or a prolongation of survival in a subject (*i.e.*, a human patient). The results may require multiple doses of the compound.

[0041] “Treating” or “treatment” of a disease in a subject refers to 1) preventing the disease from occurring in a patient that is predisposed or does not yet display symptoms of the disease; 2) inhibiting the disease or arresting its development; or 3) ameliorating or causing regression of the disease. As used herein, “treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. For the purposes of this disclosures, beneficial or desired results include, but are not limited to, one or more of the following: decreasing one or more symptoms resulting from the disease or disorder, diminishing the extent of the disease or disorder, stabilizing the disease or disorder (*e.g.*, preventing or delaying the worsening of the disease or disorder), delaying the occurrence or recurrence of the disease or disorder, delaying or slowing the progression of the disease or disorder, ameliorating the disease or disorder state, providing a remission (whether partial or total) of the disease or disorder, decreasing the dose of one or more other medications required to treat the disease or disorder, enhancing the effect of another medication used to treat the disease or disorder, delaying the progression of the disease or disorder, increasing the quality of life, and/or prolonging survival of a subject. Also encompassed by “treatment” is a reduction of pathological consequence of the disease or

disorder. The methods of the invention contemplate any one or more of these aspects of treatment.

[0042] As used herein, the terms “individual(s)”, “subject(s)” and “patient(s)” mean any mammal. Examples include, but are not limited to, mice, rats, hamsters, guinea pigs, pigs, rabbits, cats, dogs, goats, sheep, cows, and humans. In some embodiments, the mammal is a human.

[0043] A “therapeutic effect”, as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described herein. A therapeutic effect includes delaying or eliminating the appearance of a disease or condition; delaying or eliminating the onset of symptoms of a disease or condition; slowing, halting, or reversing the progression of a disease or condition; causing partial or complete regression of a disease or condition; or any combination thereof.

[0044] The terms “co-administration,” “administered in combination with,” and their grammatical equivalents, as used herein, encompass administration of two or more agents to an animal, including humans, so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[0045] “Pharmaceutically acceptable” refers to compounds, salts, compositions, dosage forms, and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0046] “Pharmaceutically acceptable salt” includes both acid and base addition salts.

[0047] “Pharmaceutically acceptable acid addition salt” refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-

oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

[0048] “Pharmaceutically acceptable base addition salt” refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

[0049] In some embodiments, pharmaceutically acceptable salts include quaternary ammonium salts such as quaternary amine alkyl halide salts (*e.g.*, methyl bromide).

[0050] As used herein, “therapeutic agent” refers to a biological, pharmaceutical, or chemical compound or other moiety. Non-limiting examples include a simple or complex organic or inorganic molecule, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, antibody fragment, a vitamin derivative, a carbohydrate, a toxin, or a chemotherapeutic compound. Various compounds can be synthesized, for example, small molecules and oligomers (*e.g.*, oligopeptides and oligonucleotides), and synthetic organic compounds based on various core structures. In addition, various natural sources can provide compounds for screening, such as plant or animal extracts, and the like.

[0051] The term “*in vivo*” refers to an event that takes place in a subject’s body.

[0052] Embodiments of the disclosure are also meant to encompass all pharmaceutically acceptable compounds of Formula (I) being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number (*i.e.*, an “isotopic form” of a compound of Formula (I)). Examples of isotopes that can be incorporated into the compounds of Formula (I) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of Formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.*, ^3H , and carbon-14, *i.e.*, ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[0053] Substitution with heavier isotopes such as deuterium, *i.e.*, ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence are preferred in some circumstances.

[0054] Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0055] Certain embodiments are also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the embodiments include compounds produced by a process comprising administering a compound of this disclosure to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabeled compound of the disclosure in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood, or other biological samples.

[0056] “Stable compound” and “stable structure” are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0057] Often crystallizations produce a solvate of the compound of the disclosure. As used herein, the term “solvate” refers to an aggregate that comprises one or more molecules of a compound of Formula (I) with one or more molecules of solvent. In some embodiments, the solvent is water, in which case the solvate is a hydrate. Alternatively, in other embodiments, the solvent is an organic solvent. Thus, the compounds of Formula (I) may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. In some aspects, the compound of Formula (I) is a true solvate, while in other cases, the compound of the disclosure merely retains adventitious water or is a mixture of water plus some adventitious solvent.

[0058] “Optional” or “optionally” means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, “optionally substituted aryl” means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution. Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Similarly, the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan.

[0059] A “pharmaceutical composition” or “pharmaceutically acceptable composition” refers to a formulation of a compound of the disclosure and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents, or excipients therefor.

[0060] “Pharmaceutically acceptable carrier, diluent or excipient” includes, without limitation, any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0061] The compounds of Formula (I), or a pharmaceutically acceptable salt or isotopic form thereof, may contain one or more centers giving rise to geometric asymmetry and may thus provide enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or (*L*)- for amino acids. Embodiments thus include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0062] A “stereoisomer” refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes “enantiomers”, which refers to two stereoisomers whose molecules are non-superimposable mirror images of one another.

[0063] “Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0064] A “tautomer” refers to a proton shift from one atom of a molecule to another atom of the same molecule. Embodiments thus include tautomers of the disclosed compounds.

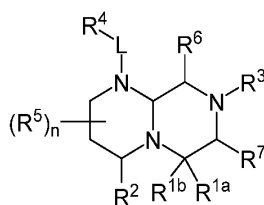
[0065] The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program and/or ChemDraw Ultra Version 11.0.1 software naming program (CambridgeSoft). For complex chemical names employed herein, a substituent group is typically named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with a cyclopropyl substituent. Except as described below, all bonds are identified in the chemical structure diagrams herein, except for all bonds on some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

[0066] Although various features of the invention may be described in the context of a single embodiment, the features may also be provided separately or in any suitable combination. Conversely, although the invention may be described herein in the context of separate embodiments for clarity, the invention may also be implemented in a single embodiment.

Compounds

[0067] The compounds of Formula (I), or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, and methods of preparing the same are described in PCT Publication WO2022/094400, which is incorporated herein by reference in its entirety for any purpose.

[0068] In one aspect, provided herein is a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, wherein:

L is a direct bond, $-C(=O)-$, $-(CR^aR^b)_m-C(=O)-$, $-C(=O)-(CR^aR^b)_m-$, or $-(CR^aR^b)_m-$;

each R^a and R^b is independently H, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;

R^{1a} and R^{1b} are independently H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halo, or C₆-C₁₀ arylalkyl;

R^2 is H, oxo, or thioxo;

R^3 is C₂-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₁₂ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₆-C₁₀ arylalkyl, 5- to 10-membered heteroarylalkyl, or 5- to 10-membered heterocyclylalkyl,

wherein the 5- to 10-membered heteroarylalkyl or 5- to 10-membered heterocyclylalkyl contains 1-3 heteroatoms selected from nitrogen and oxygen;

R^4 is C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, or 5- to 10-membered heterocyclyl,

wherein the 5- to 10-membered heteroaryl or 5- to 10-membered heterocyclyl contains 1-3 heteroatoms selected from nitrogen and oxygen;

each R⁵ is independently C₁-C₆ alkyl, oxo, or halo;

R⁶ is H, C₁-C₆ alkyl, or oxo;

R⁷ is H or oxo;

m is 1 or 2; and

n is an integer from 0 to 3;

wherein each C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkylalkyl, C₆-C₁₀ aryl, C₆-C₁₀ arylalkyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroarylalkyl, 5- to 10-membered heterocyclyl, and 5- to 10-membered heterocyclylalkyl is optionally substituted with one to five substituents selected from hydroxyl, halo, amino, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, cyano, -(C=O)NH₂, nitro, -SO₂(C₁-C₆ alkyl), and -CO₂H.

[0069] In some embodiments, L is a direct bond. In some embodiments, L is -C(=O)- or -(CR^aR^b)_m-. In some embodiments, L is -C(=O)-. In some embodiments, L is -(CR^aR^b)_m-. In some embodiments, L is -(CR^aR^b)_m-C(=O)- or -C(=O)-(CR^aR^b)_m-. In some embodiments, L is -(CR^aR^b)_m-C(=O)-. In some embodiments, L is -C(=O)-(CR^aR^b)_m-.

[0070] In some embodiments, each R^a and R^b is independently H, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl. In some embodiments, each R^a and R^b is independently H, C₁-C₃ alkyl, C₂-C₄ alkenyl, or C₂-C₄ alkynyl. In some embodiments, R^a and R^b are each H. In some embodiments, R^a is H. In some embodiments, R^a is C₁-C₆ alkyl, such as methyl, ethyl, or propyl. In some embodiments, R^a is C₂-C₆ alkenyl, such as vinyl or propenyl. In some embodiments, R^a is C₂-C₆ alkynyl, such as ethynyl or propynyl. In some embodiments, R^b is H. In some embodiments, R^b is C₁-C₆ alkyl, such as methyl, ethyl, or propyl. In some embodiments, R^b is C₂-C₆ alkenyl, such as vinyl or propenyl. In some embodiments, R^b is C₂-C₆ alkynyl, such as ethynyl or propynyl.

[0071] In some embodiments, R^{1a} and R^{1b} are independently H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halo, or C₆-C₁₀ arylalkyl. In some embodiments, R^{1a} is H. In some embodiments, R^{1a} is C₁-C₆ alkyl, such as methyl, ethyl, or propyl. In some embodiments, R^{1a} is C₂-C₆ alkenyl, such as vinyl or propenyl. In some embodiments, R^{1a} is C₂-C₆ alkynyl, such as ethynyl or propynyl. In some embodiments, R^{1a} is C₁-C₆ alkoxy, such as methoxy, ethoxy, or propoxy. In some embodiments, R^{1a} is halo, such as fluoro, chloro, or bromo. In some embodiments, R^{1a} is C₆-C₁₀ arylalkyl, such as benzyl. In some embodiments, R^{1b} is H. In

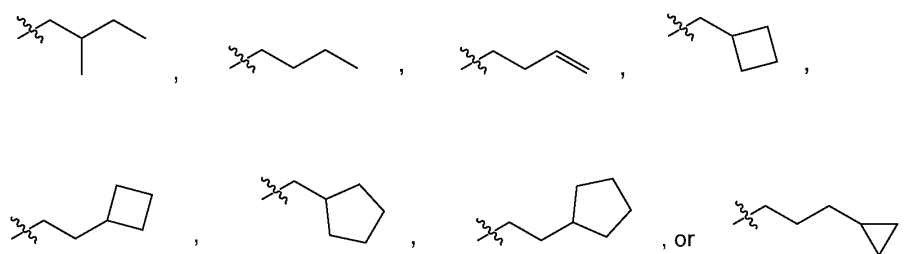
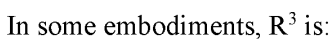
some embodiments, R^{1b} is C₁-C₆ alkyl, such as methyl, ethyl, or propyl. In some embodiments, R^{1b} is C₂-C₆ alkenyl, such as vinyl or propenyl. In some embodiments, R^{1b} is C₂-C₆ alkynyl, such as ethynyl or propynyl. In some embodiments, R^{1b} is C₁-C₆ alkoxy, such as methoxy, ethoxy, or propoxy. In some embodiments, R^{1b} is halo, such as fluoro, chloro, or bromo. In some embodiments, R^{1b} is C₆-C₁₀ arylalkyl, such as benzyl.

[0072] In some embodiments, R^{1a} and R^{1b} are each independently H; C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from halo, -CO₂H, and -C(=O)NH₂; C₁-C₆ alkoxy; halo; or C₆-C₁₀ arylalkyl optionally substituted by 1-3 substituents selected from halo and amino. In some embodiments, R^{1a} is C₁-C₆ alkyl substituted with 1-3 halo, such as fluoro or chloro. In some embodiments, R^{1a} is C₁-C₆ alkyl substituted with 1-3 -CO₂H groups. In some variations, R^{1a} is C₁-C₃ alkyl substituted with 1-2 CO₂H groups, such as -CH₂CO₂H or -CH₂CH₂CO₂H. In some embodiments, R^{1a} is C₁-C₆ alkyl substituted with 1-3 -C(=O)NH₂ groups. In some embodiments, R^{1a} is C₁-C₃ alkyl substituted with 1-2 -C(=O)NH₂ groups, such as -CH₂C(=O)NH₂ or -CH₂CH₂C(=O)NH₂. In some embodiments, R^{1a} is C₆-C₁₀ arylalkyl substituted by 1-3 substituents selected from halo and amino. In some embodiments, R^{1a} is C₆-C₁₀ arylalkyl substituted by 1-3 halo, such as fluoro, chloro, or bromo. In some embodiments, R^{1a} is C₆-C₁₀ arylalkyl substituted by 1-3 amino. In some embodiments, R^{1b} is C₁-C₆ alkyl substituted with 1-3 halo, such as fluoro or chloro. In some embodiments, R^{1b} is C₁-C₆ alkyl substituted with 1-3 -CO₂H groups. In some variations, R^{1b} is C₁-C₃ alkyl substituted with 1-2 -CO₂H groups, such as -CH₂CO₂H or -CH₂CH₂CO₂H. In some embodiments, R^{1b} is C₁-C₆ alkyl substituted with 1-3 -C(=O)NH₂ groups. In some embodiments, R^{1b} is C₁-C₃ alkyl substituted with 1-2 -C(=O)NH₂ groups, such as -CH₂C(=O)NH₂ or -CH₂CH₂C(=O)NH₂. In some embodiments, R^{1b} is C₆-C₁₀ arylalkyl substituted by 1-3 substituents selected from halo and amino. In some embodiments, R^{1b} is C₆-C₁₀ arylalkyl substituted by 1-3 halo, such as fluoro, chloro, or bromo. In some embodiments, R^{1b} is C₆-C₁₀ arylalkyl substituted by 1-3 amino. In some embodiments, R^{1a} and R^{1b} are each independently H, methyl, fluoro, 2-methylbutyl, -CH₂F, methoxy, -CH₂CO₂H, -CH₂C(=O)NH₂, benzyl, or 4-aminobenzyl. In some embodiments, R^{1a} and R^{1b} are each independently H or C₁-C₃ alkyl. In some embodiments, R^{1a} is methyl and R^{1b} is H. In some embodiments, R^{1a} and R^{1b} are each H. In some embodiments, one of R^{1a} and R^{1b} is H and the other is C₁-C₃ alkyl, such as methyl.

[0073] In some embodiments, R² is H, oxo, or thioxo. In some embodiments, R² is H. In some embodiments, R² is oxo. In some embodiments, R² is thioxo.

[0074] In some embodiments, R^3 is C₃-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₁₂ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₆-C₁₀ arylalkyl, 5- to 10-membered heteroarylalkyl, or 5- to 10-membered heterocyclylalkyl, wherein the 5- to 10-membered heteroarylalkyl or 5- to 10-membered heterocyclylalkyl contains 1-3 heteroatoms selected from nitrogen and oxygen. In some embodiments, R^3 is C₃-C₆ alkyl, such as propyl, butyl, pentyl, or hexyl. In some embodiments, R^3 is C₄-C₆ alkyl. In some embodiments, R^3 is C₃-C₆ alkenyl. In some embodiments, R^3 is C₄-C₆ alkenyl. In some embodiments, R^3 is C₃-C₆ alkynyl. In some embodiments, R^3 is C₄-C₆ alkynyl. In some embodiments, R^3 is C₃-C₁₂ cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, R^3 is C₃-C₆ cycloalkyl. In some embodiments, R^3 is C₃-C₆ cycloalkylalkyl, such as $-(CH_2)_{1-3}(C_3-C_6 \text{ cycloalkyl})$. In some embodiments, R^3 is C₆-C₁₀ arylalkyl, such as benzyl. In some embodiments, R^3 is 5- to 10-membered heteroarylalkyl, such as $-(CH_2)_{1-3}(5\text{- to }10\text{-membered heteroaryl})$ or $-(CH_2)_{1-3}(5\text{- to }6\text{-membered heteroaryl})$. In some embodiments, the 5- to 10-membered heteroarylalkyl contains 1-2 nitrogen atoms. In some embodiments, R^3 is 5- to 10-membered heterocyclylalkyl, such as $-(CH_2)_{1-3}(5\text{- to }10\text{-membered heterocyclyl})$ or $-(CH_2)_{1-2}(5\text{- to }6\text{-membered heterocyclyl})$. In some embodiments, the 5- to 10-membered heterocyclylalkyl contains 1-2 nitrogen atoms.

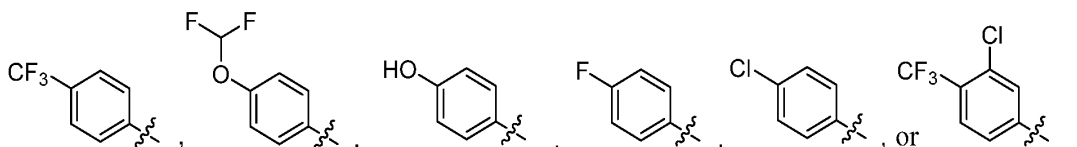
[0075] In some embodiments, R^3 is C₃-C₆ alkyl optionally substituted by 1-3 substituents selected from halo and $-C(=O)NH_2$, C₂-C₆ alkenyl, or C₃-C₆ cycloalkylalkyl. In some embodiments, R^3 is C₂-C₆ alkyl optionally substituted by 1-3 substituents selected from halo, C₁-C₃ alkoxy, hydroxy, $-NH_2$, $-SO_2(C_1-C_3 \text{ alkyl})$, and $-C(=O)NH_2$; C₂-C₆ alkenyl; C₃-C₆ cycloalkylalkyl; 5- to 6-membered heteroarylalkyl; 5- to 6-membered heterocyclylalkyl; or C₆ arylalkyl. In some embodiments, R^3 is C₂ alkyl substituted by 1-3 substituents selected from C₁-C₃ alkoxy, hydroxy, $-NH_2$, and $-SO_2(C_1-C_3 \text{ alkyl})$. In some embodiments, R^3 is:



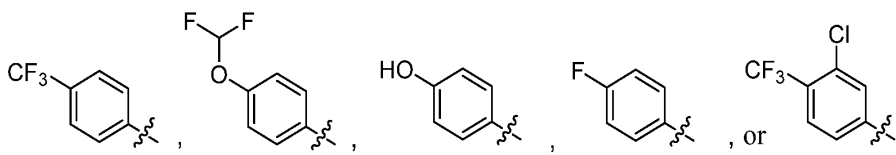
[0076] In some embodiments, R⁴ is C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, or 5- to 10-membered heterocyclyl, wherein the 5- to 10-membered heteroaryl or 5- to 10-membered heterocyclyl contains 1-3 heteroatoms selected from nitrogen and oxygen. In some embodiments, R⁴ is C₆-C₁₀ aryl, such as phenyl. In some embodiments, R⁴ is 5- to 10-membered heteroaryl containing 1-2 nitrogen atoms. In some embodiments, R⁴ is 5- to 10-membered heterocyclyl. In some embodiments, R⁴ is 5- to 9-membered heterocyclyl

containing 1-2 nitrogen atoms. In some embodiments, R^4 is 5- to 9-membered heterocyclyl containing 1-2 oxygen atoms. In some embodiments, R^4 is 5- to 9-membered heterocyclyl containing 1 nitrogen atom and 1 oxygen atom.

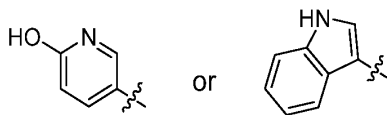
[0077] In some embodiments, R^4 is C_6 - C_{10} aryl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1 - C_6 haloalkyl, and C_1 - C_6 haloalkoxy. In some embodiments, R^4 is phenyl substituted with 1-3 substituents selected from $-CF_3$, $-OCHF_2$, $-OH$, fluoro, and chloro. In some embodiments, R^4 is:



In some embodiments, R^4 is:



[0078] In some embodiments, R^4 is 5- to 10-membered heteroaryl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1 - C_6 haloalkyl, and C_1 - C_6 haloalkoxy. In some embodiments, R^4 is pyridyl or indolyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1 - C_6 haloalkyl, and C_1 - C_6 haloalkoxy. In some embodiments, R^4 is



In some embodiments, R^4 is pyridyl substituted with 1-3 substituents selected from halo, hydroxyl, C_1 - C_6 haloalkyl, and C_1 - C_6 haloalkoxy. In some

embodiments, R^4 is

Chemical structure for R^4 : 3-hydroxypyridyl.

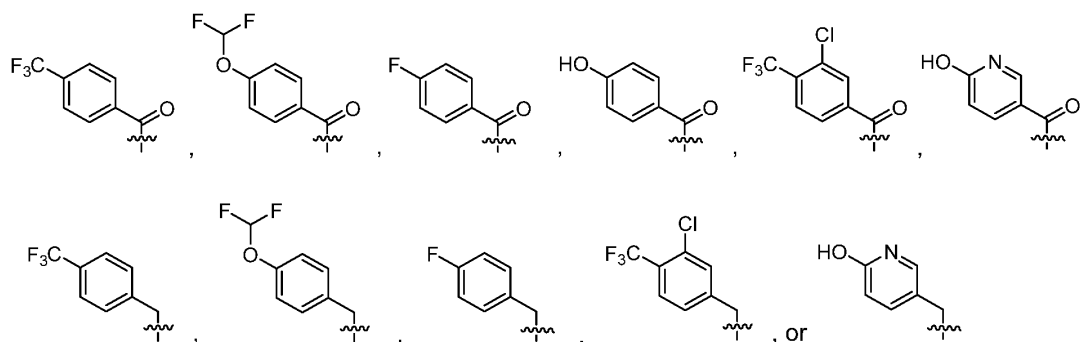
In some embodiments, R^4 is 5- to 10-membered heterocyclyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1 - C_6

haloalkyl, and C_1 - C_6 haloalkoxy. In some embodiments, R^4 is indolyl.

Chemical structure for R^4 : indolyl.

[0079] In some embodiments, $-L-R^4$ is $-CH_2$ (phenyl) or $-C(O)$ (phenyl), wherein the phenyl is substituted by 1-3 substituents selected from C_1 - C_3 haloalkyl, C_1 - C_3 haloalkoxy, halo, and

hydroxy. In some embodiments, $-L-R^4$ is $-\text{CH}_2(\text{pyridyl})$ or $-\text{C}(\text{O})(\text{pyridyl})$, wherein the pyridyl is substituted by 1-3 substituents selected from $\text{C}_1\text{-C}_3$ haloalkyl, $\text{C}_1\text{-C}_3$ haloalkoxy, halo, and hydroxy. In some embodiments, $-L-R^4$ is:



[0080] In some embodiments, each R^5 is independently $\text{C}_1\text{-C}_6$ alkyl, oxo, or halo. In some embodiments, R^5 is $\text{C}_1\text{-C}_6$ alkyl, such as methyl, ethyl, or propyl. In some embodiments, R^5 is oxo. In some embodiments, R^5 is halo, such as fluoro, chloro, or bromo. In some embodiments, R^5 is oxo or halo. In some embodiments, R^5 is oxo or fluoro.

[0081] In some embodiments, R^6 is H, $\text{C}_1\text{-C}_6$ alkyl, or oxo. In some embodiments, R^6 is H. In some embodiments, R^6 is $\text{C}_1\text{-C}_6$ alkyl, such as methyl, ethyl, or propyl. In some embodiments, R^6 is oxo.

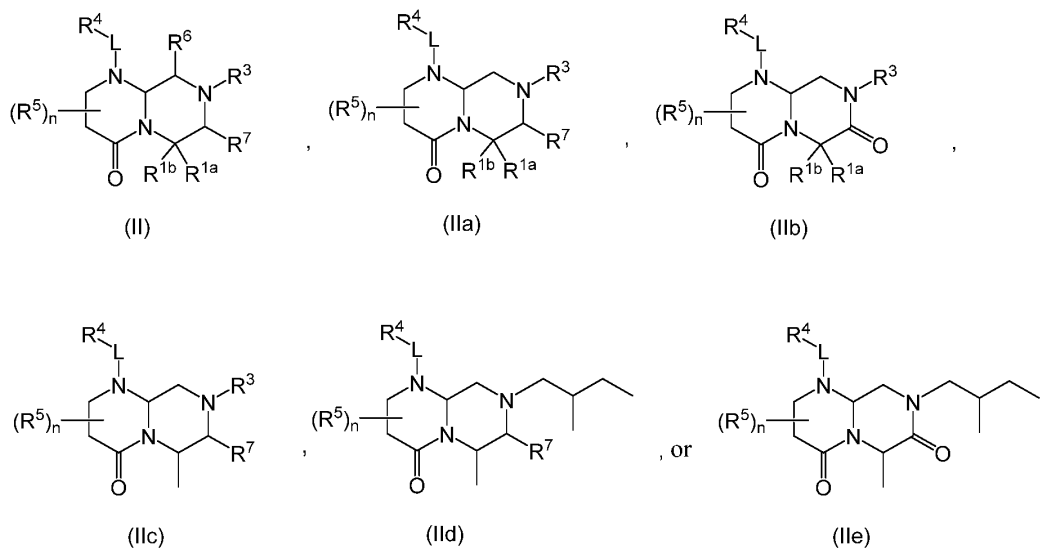
[0082] In some embodiments, R^7 is H or oxo. In some embodiments, R^7 is H. In some embodiments, R^7 is oxo.

[0083] In some embodiments, m is 1. In other embodiments, m is 2.

[0084] In some embodiments, n is 0. In other embodiments, n is an integer from 1 to 3. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3.

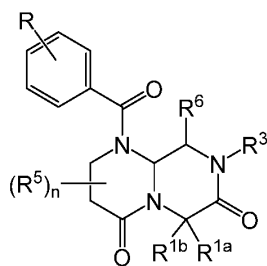
[0085] In any embodiments of Formula (I), or variations thereof, each $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_{12}$ cycloalkyl, $\text{C}_3\text{-C}_{12}$ cycloalkylalkyl, $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_6\text{-C}_{10}$ arylalkyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroarylalkyl, 5- to 10-membered heterocyclyl, and 5- to 10-membered heterocyclylalkyl is optionally substituted with one to three substituents selected from hydroxyl, halo (such as fluoro, chloro, or bromo), amino, $\text{C}_1\text{-C}_6$ haloalkyl (such as $-\text{CF}_3$ or $-\text{CHF}_2$), $\text{C}_1\text{-C}_6$ alkoxy (such as methoxy or ethoxy), $\text{C}_1\text{-C}_6$ haloalkoxy (such as $-\text{OCHF}_2$ or $-\text{OCF}_3$), and $-(\text{C}=\text{O})\text{NH}_2$.

[0086] In some embodiments, the compound of Formula (I) is a compound of Formula (II), (IIa), (IIb), (IIc), (IId), or (IIe):

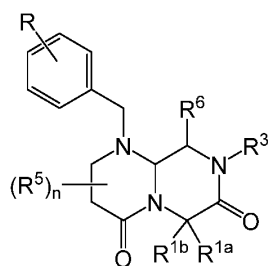


or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, wherein L, R^{1a} , R^{1b} , R^3 , R^4 , R^5 , R^6 , R^7 , and n are as described for Formula (I). In some embodiments, the compound is of Formula (II) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IIa) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IIb) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IIc) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IId) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IIe) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

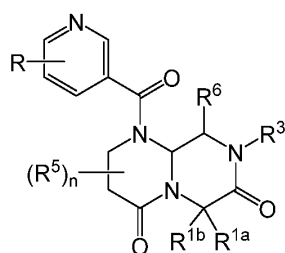
[0087] In some embodiments, the compound of Formula (I) is a compound of Formula (IIIa), (IIIb), (IIIc), or (IIId):



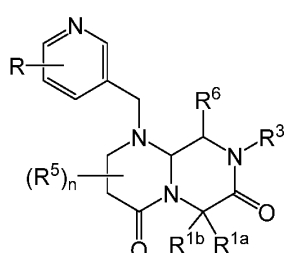
(IIIa)



(IIIb)



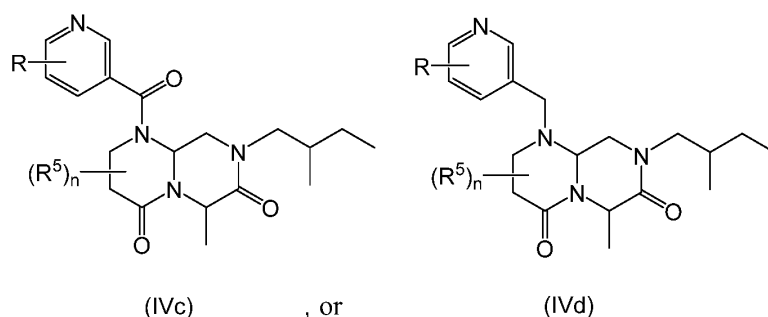
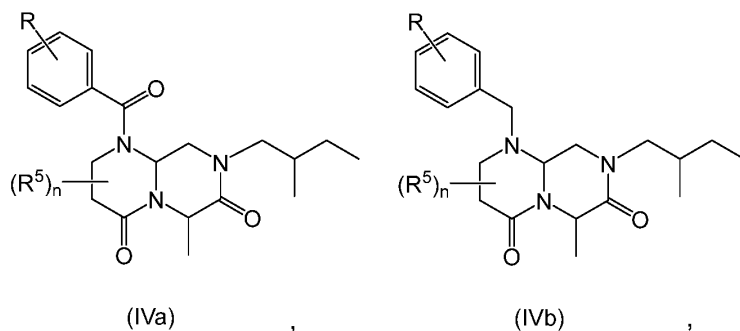
(IIIc)



(IIId)

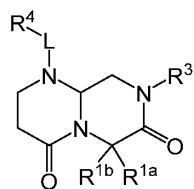
or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, wherein R^{1a} , R^{1b} , R^3 , R^5 , R^6 , and n are as described for Formula (I), and R represents one or more optional substituents, such as hydroxyl, halo, amino, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, as described for Formula (I). In some embodiments, the compound is of Formula (IIIa) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IIIb) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IIIc) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IIId) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

[0088] In some embodiments, the compound of Formula (I) is a compound of Formula (IVa), (IVb), (IVc), or (IVd):



or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, wherein R^5 and n are as described for Formula (I), and R represents one or more optional substituents, such as hydroxyl, halo, amino, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, as described for Formula (I). In some embodiments, the compound is of Formula (IVa) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IVb) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IVc) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, the compound is of Formula (IVd) or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

[0089] In some embodiments, the compound of Formula (I) is a compound of Formula (V):



(V)

or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, wherein L , R^{1a} , R^{1b} , R^3 , and R^4 are as described for Formula (I). In some embodiments, L is $-C(=O)-$ or $-CH_2-$;

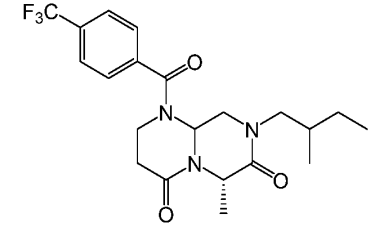
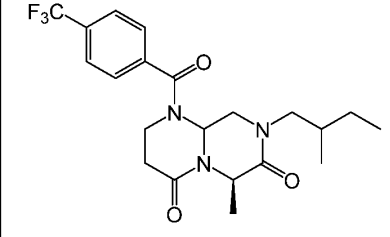
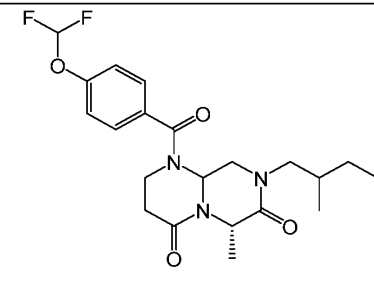
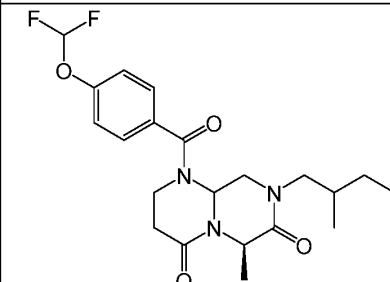
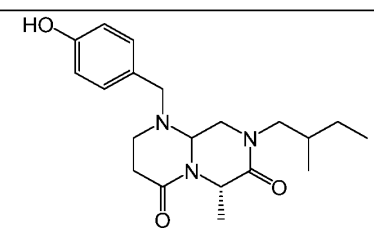
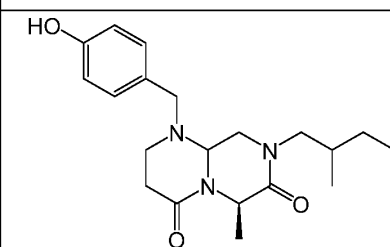
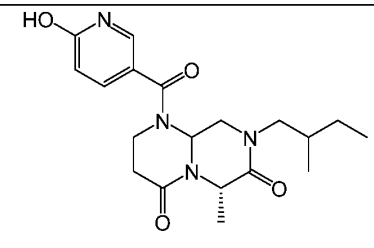
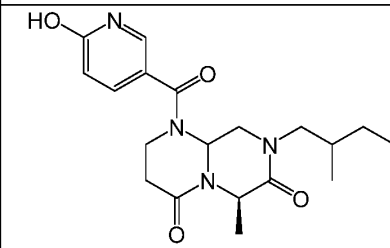
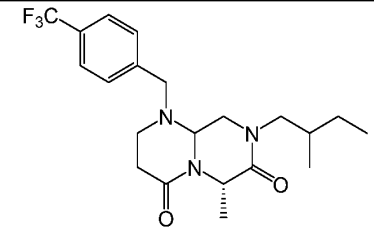
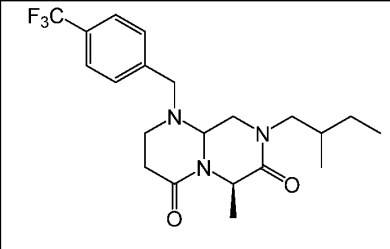
R^{1a} and R^{1b} are independently H or C₁-C₃ alkyl optionally substituted with -CO₂H; R³ is C₄-C₅ alkyl, C₄-C₅ alkenyl, or C₁-C₃ alkyl substituted with C₃-C₅ cycloalkyl; and R⁴ is phenyl or pyridyl substituted with 1-3 substituents selected from -CF₃, -OCHF₂, -OH, fluoro, and chloro. In some variations, one of R^{1a} and R^{1b} is H and the other is C₁-C₃ alkyl, such as methyl.

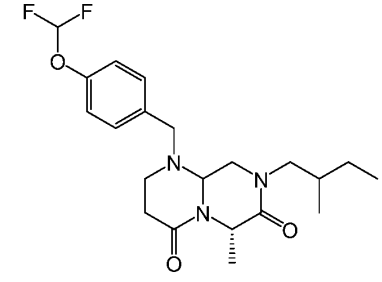
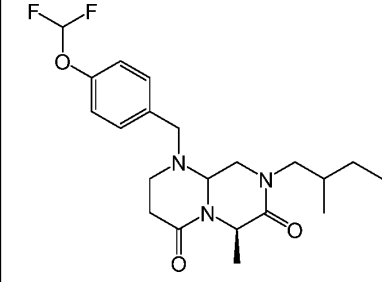
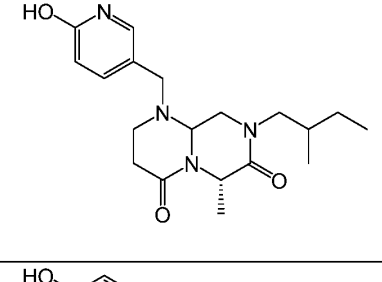
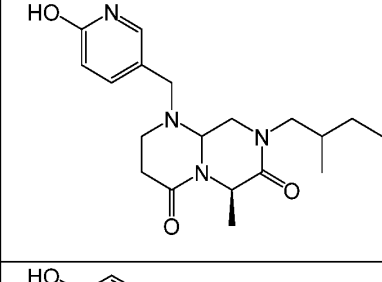
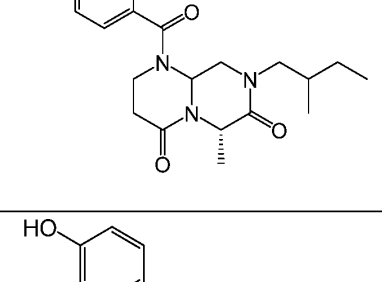
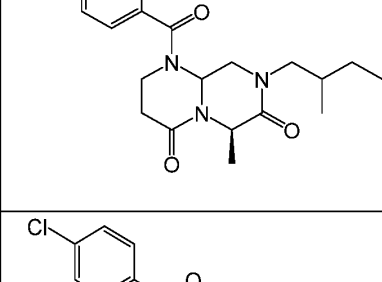
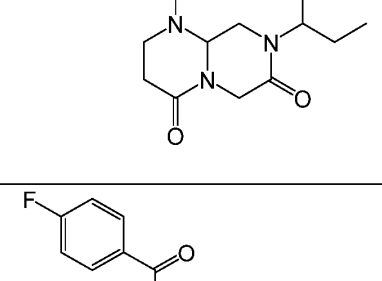
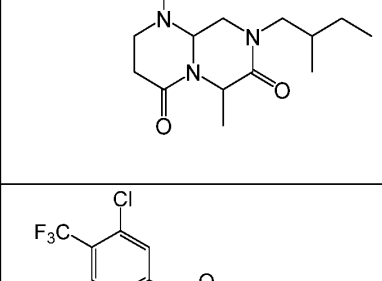
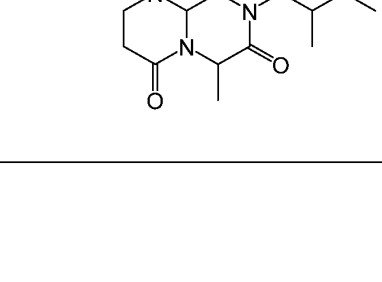
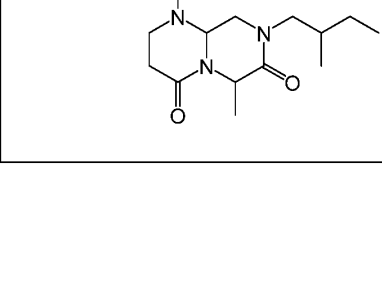
[0090] In the descriptions herein, it is understood that every description, variation, embodiment, or aspect of a moiety may be combined with every description, variation, embodiment, or aspect of other moieties the same as if each and every combination of descriptions is specifically and individually listed. For example, every description, variation, embodiment, or aspect provided herein with respect to L of Formula (I) may be combined with every description, variation, embodiment, or aspect of R^{1a}, R^{1b}, R², R³, R⁴, R⁵, R⁶, R⁷, and n the same as if each and every combination were specifically and individually listed. It is also understood that all descriptions, variations, embodiments, or aspects of Formula (I), where applicable, apply equally to other formulae detailed herein, and are equally described, the same as if each and every description, variation, embodiment, or aspect were separately and individually listed for all formulae. For example, all descriptions, variations, embodiments, or aspects of Formula (I), where applicable, apply equally to any of the formulae as detailed herein, such as Formulae (II), (IIa), (IIb), (IIc), (IId), (IId), (IIe), (IIIa), (IIIb), (IIIc), (IIId), (IVa), (IVb), (IVc), (IVd), and (V), and are equally described, the same as if each and every description, variation, embodiment, or aspect were separately and individually listed for all formulae.

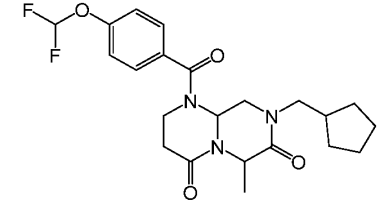
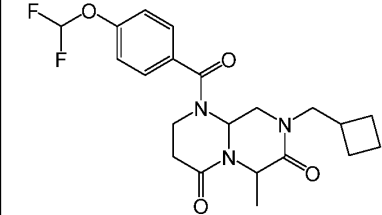
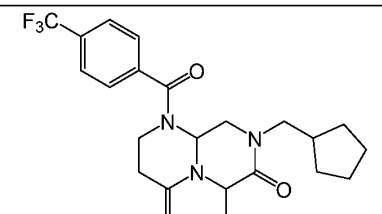
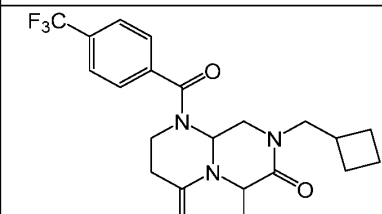
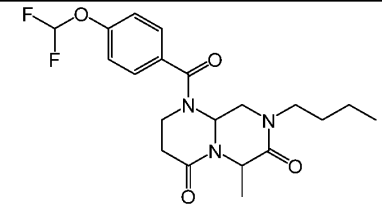
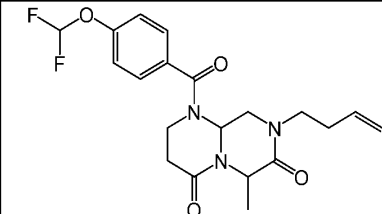
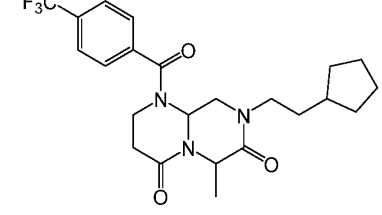
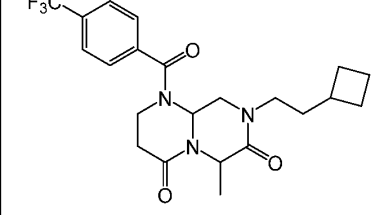
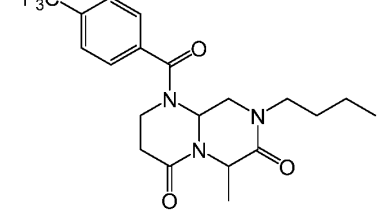
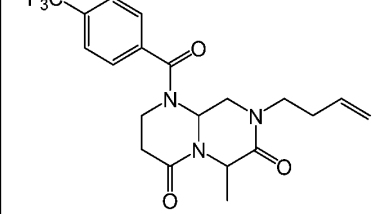
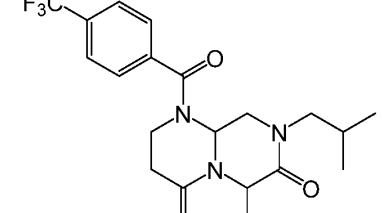
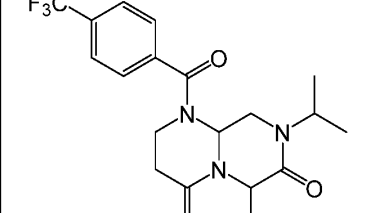
[0091] In some embodiments, provided is a compound selected from the compounds in Table 1 or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. Although certain compounds described in the present disclosure, including in Table 1, are presented as specific stereoisomers and/or in a non-stereochemical form, it is understood that any or all stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of any of the compounds of the present disclosure, including in Table 1, are herein described.

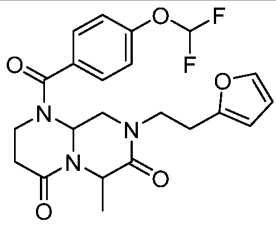
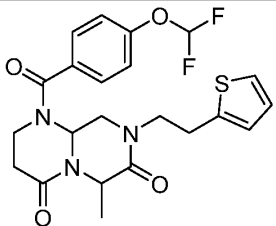
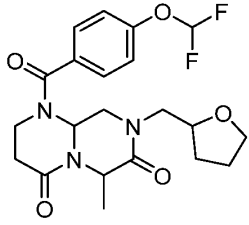
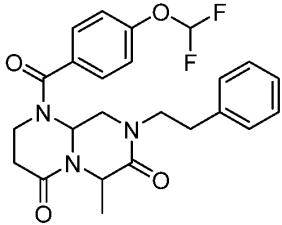
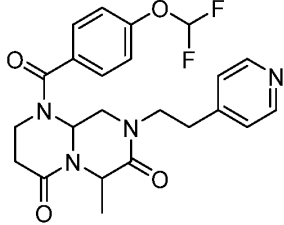
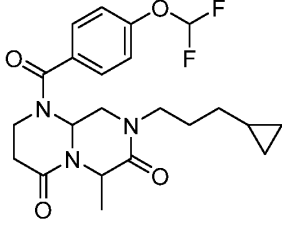
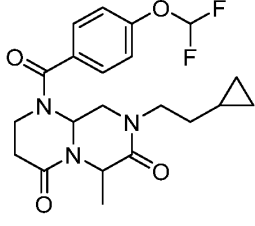
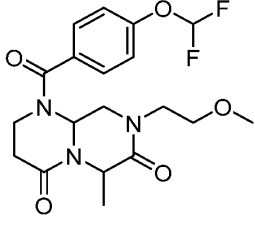
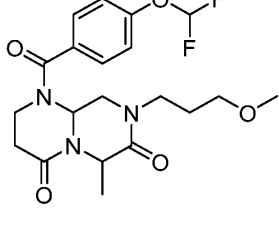
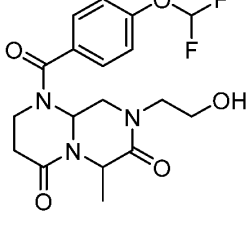
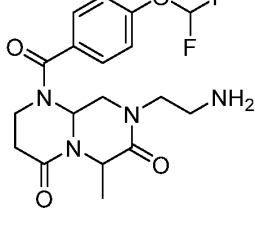
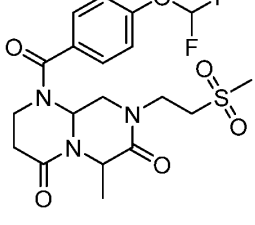
Table 1.

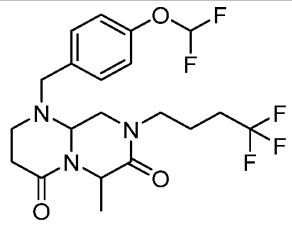
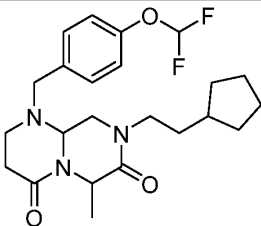
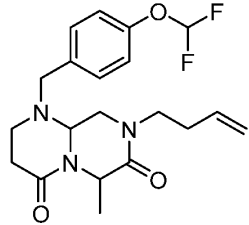
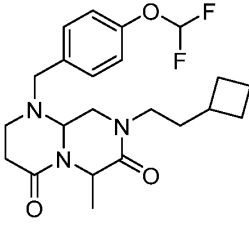
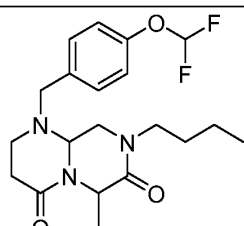
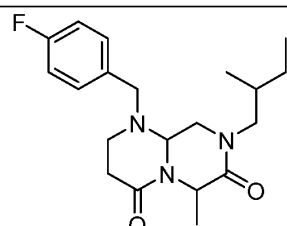
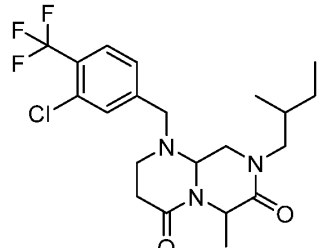
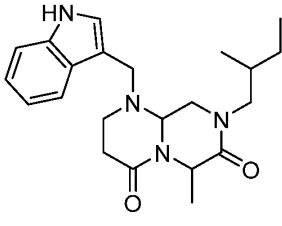
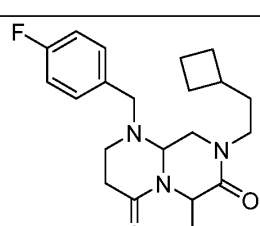
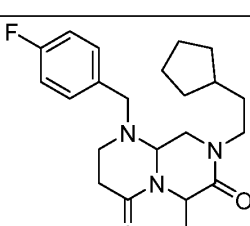
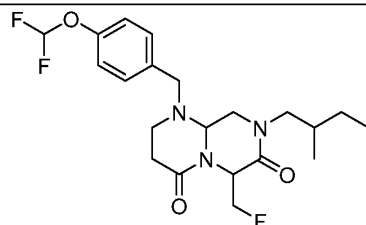
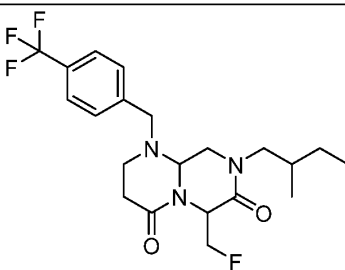
Cmpd	Structure	Cmpd	Structure
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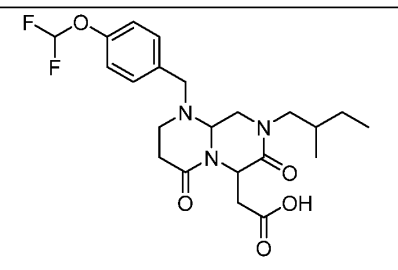
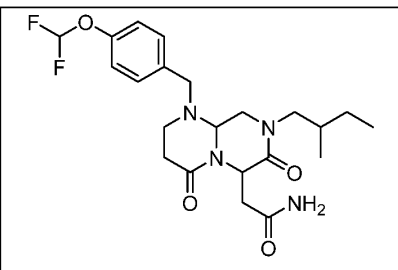
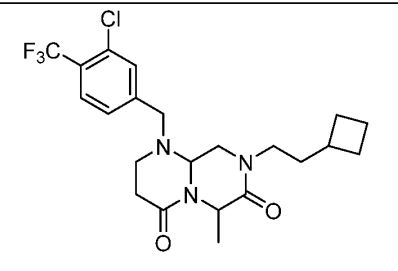
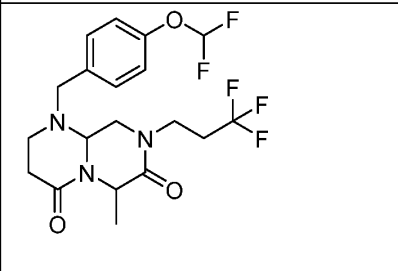
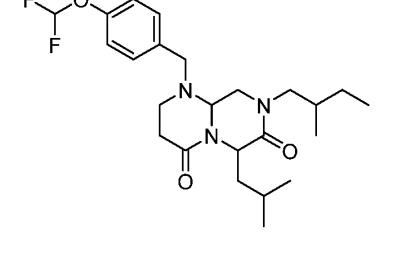
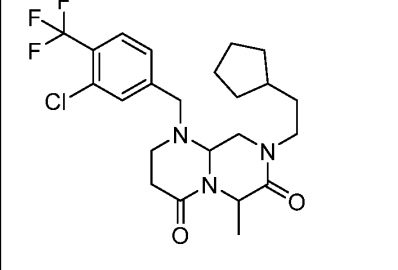
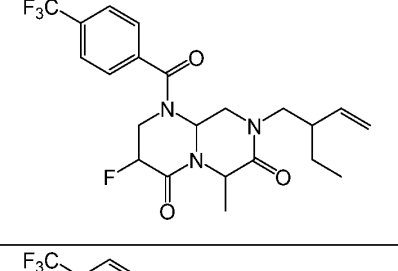
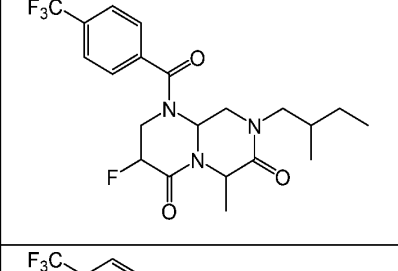
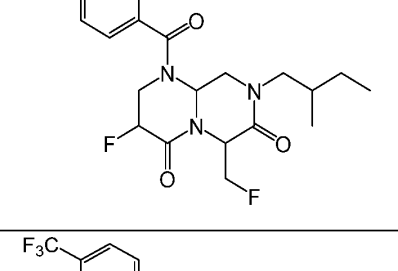
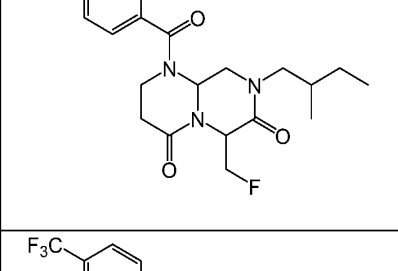
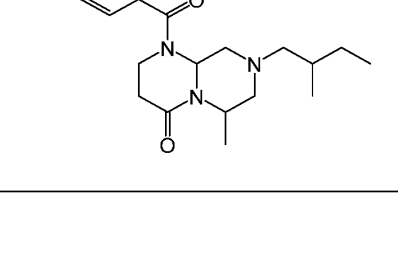
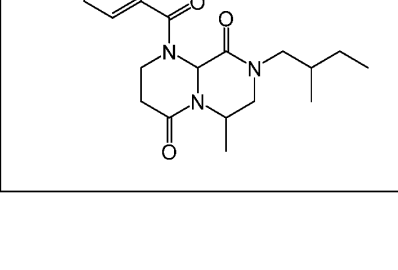
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3a		3b	
4a		4b	
5a		5b	

6a		6b	
7a		7b	
8a		8b	
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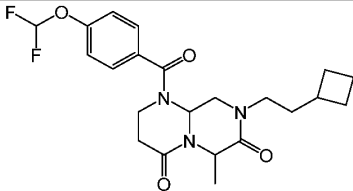
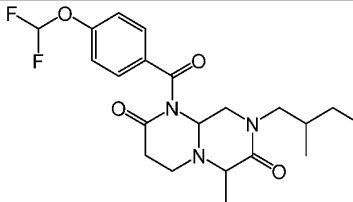
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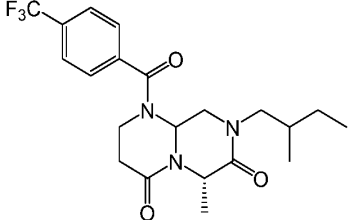
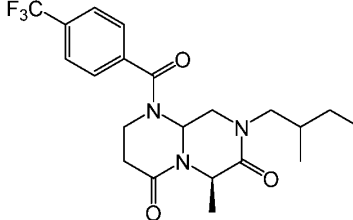
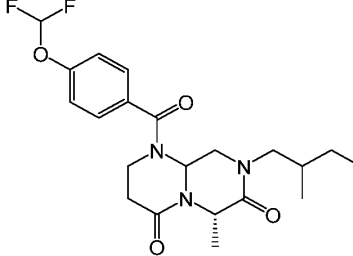
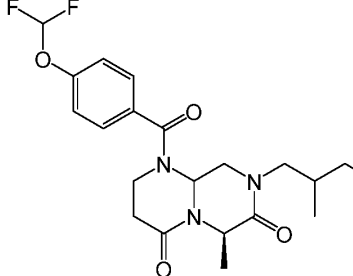
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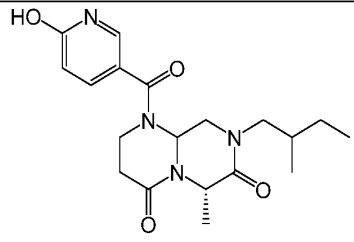
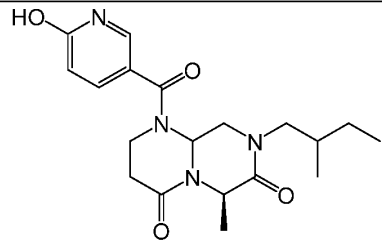
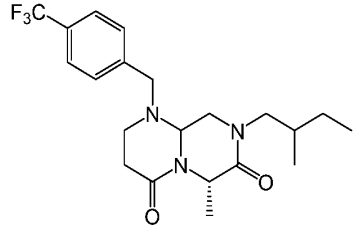
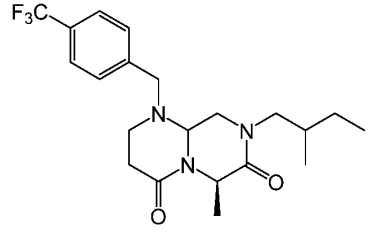
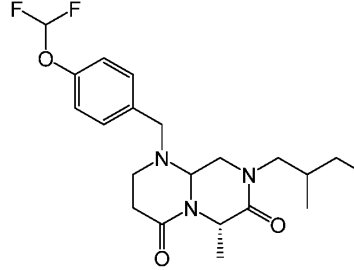
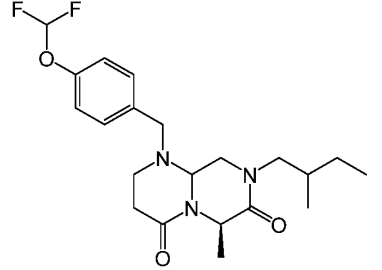
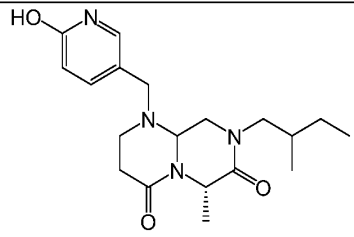
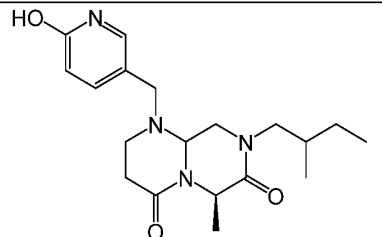
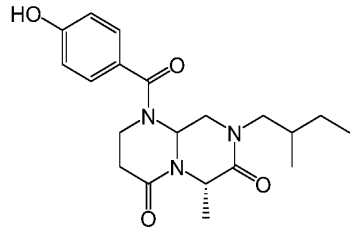
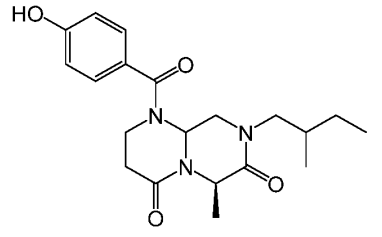
or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

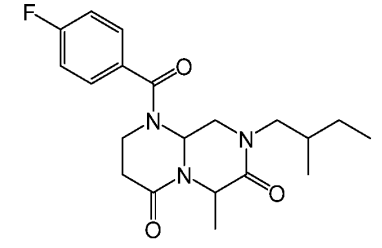
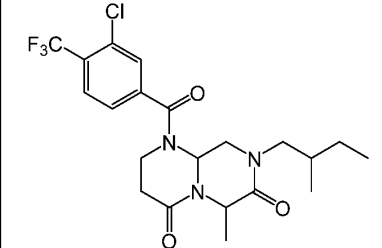
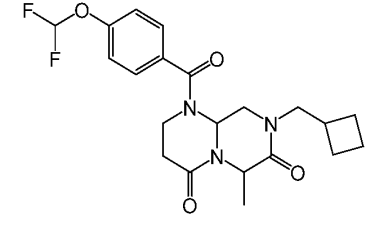
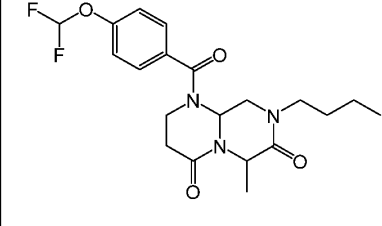
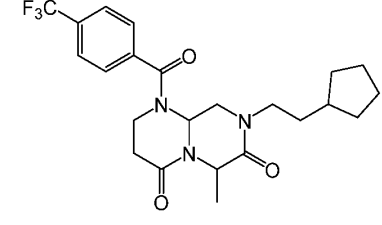
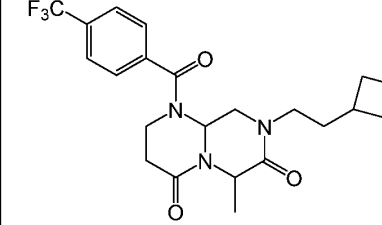
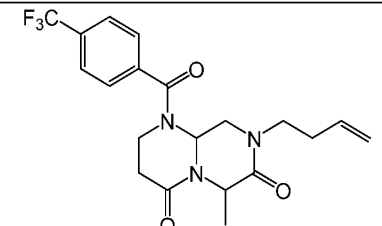
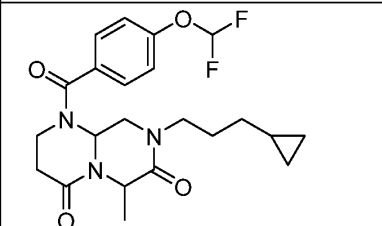
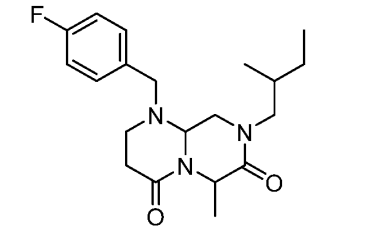
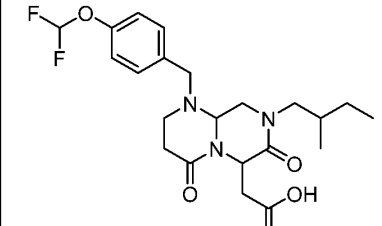
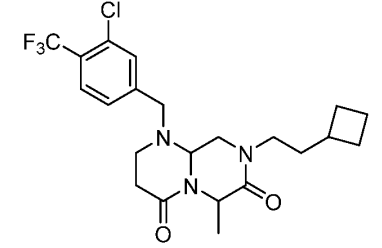
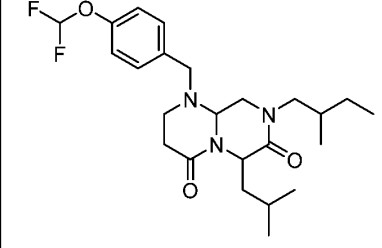
[0092] In some embodiments, the compound of Formula (I) is not Compound **3a**, **3b**, **9**, **10**, **13**, **15**, **16**, **18**, **21**, **23-29**, **31-41**, **43-48**, **50**, **52**, or **54**.

[0093] In some embodiments, provided is a compound selected from the compounds in Table 1A or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. Although certain compounds described in the present disclosure, including in Table 1A, are presented as specific stereoisomers and/or in a non-stereochemical form, it is understood that any or all stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of any of the compounds of the present disclosure, including in Table 1A, are herein described.

Table 1A.

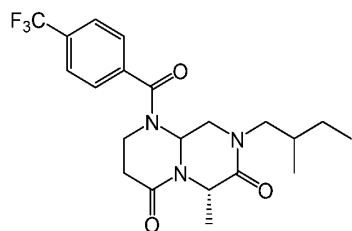
Cmpd	Structure	Cmpd	Structure
1a		1b	
2a		2b	

4a	 <chem>CC(C)CN1CC(=O)N(C(=O)N1Cc2ccc(O)nc2)CC(C)C</chem>	4b	 <chem>CC(C)CN1CC(=O)N(C(=O)N1Cc2ccc(O)nc2)CC(C)C</chem>
5a	 <chem>CC(C)CN1CC(=O)N(C(=O)N1Cc2ccc(C(F)(F)F)cc2)CC(C)C</chem>	5b	 <chem>CC(C)CN1CC(=O)N(C(=O)N1Cc2ccc(C(F)(F)F)cc2)CC(C)C</chem>
6a	 <chem>CC(C)CN1CC(=O)N(C(=O)N1Cc2ccc(OC(F)F)cc2)CC(C)C</chem>	6b	 <chem>CC(C)CN1CC(=O)N(C(=O)N1Cc2ccc(OC(F)F)cc2)CC(C)C</chem>
7a	 <chem>CC(C)CN1CC(=O)N(C(=O)N1Cc2ccc(O)nc2)CC(C)C</chem>	7b	 <chem>CC(C)CN1CC(=O)N(C(=O)N1Cc2ccc(O)nc2)CC(C)C</chem>
8a	 <chem>CC(C)CN1CC(=O)N(C(=O)N1Cc2ccc(O)cc2)CC(C)C</chem>	8b	 <chem>CC(C)CN1CC(=O)N(C(=O)N1Cc2ccc(O)cc2)CC(C)C</chem>

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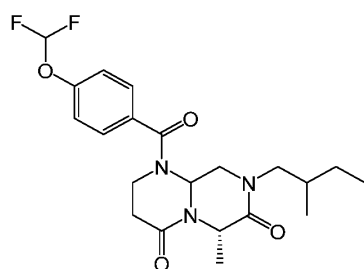
or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

[0094] In some embodiments, the compound is



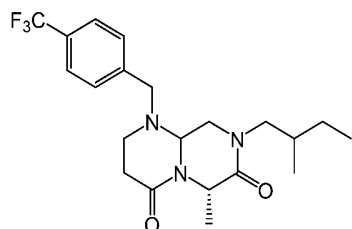
or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

[0095] In some embodiments, the compound is



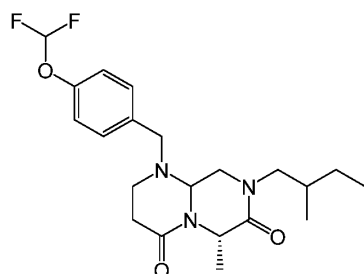
or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

[0096] In some embodiments, the compound is



or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

[0097] In some embodiments, the compound is



or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

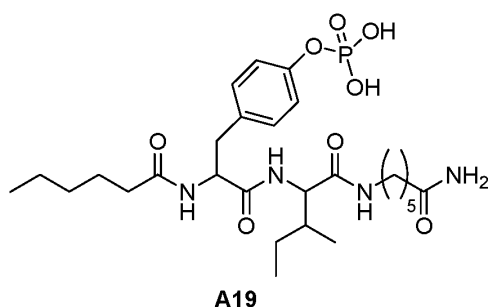
[0098] It is understood that in the present description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds.

[0099] Furthermore, all compounds of Formula (I) which exist in free base or acid form can be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic base or acid by methods known to one skilled in the art. Salts of the compounds of Formula (I) can be converted to their free base or acid form by standard techniques.

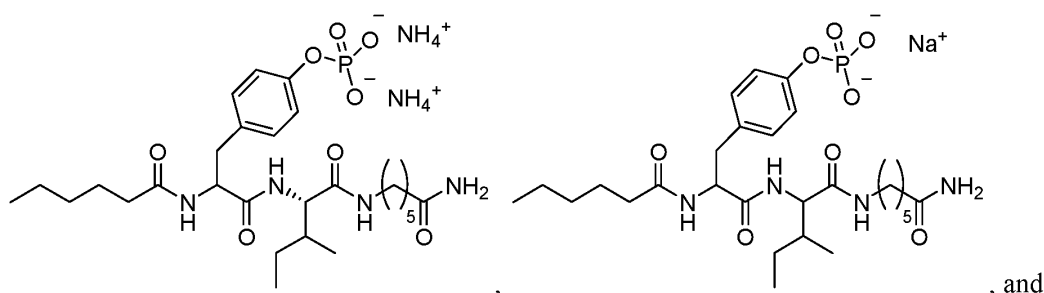
Fosgonimeton and related compounds

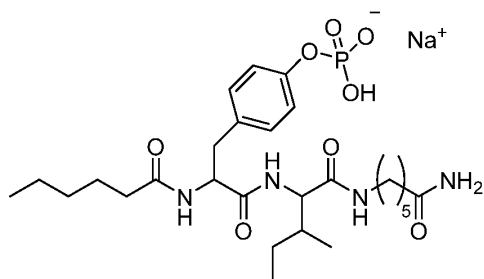
[0100] Fosgonimeton is a prodrug that is rapidly converted to the active drug ATH-1001 (Dihexa; see US2014/0094413) in the plasma after subcutaneous injection. The active drug ATH-1001 acts as a positive modulator of the hepatic growth factor (HGF) receptor and its tyrosine kinase, MET, receptor system.

[0101] Fosgonimeton is a pharmaceutically acceptable salt of the Compound A19:

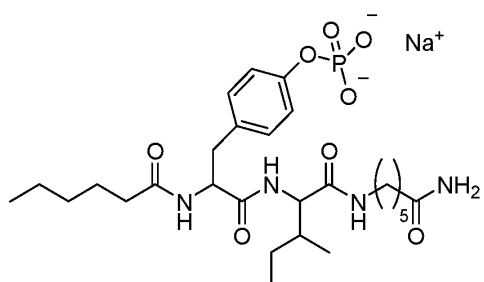


[0102] Nonlimiting exemplary pharmaceutically acceptable salts of Compound A19 include:





[0103] Unless otherwise indicated, fosgonimeton refers to the monosodium salt of Compound A19, shown below:



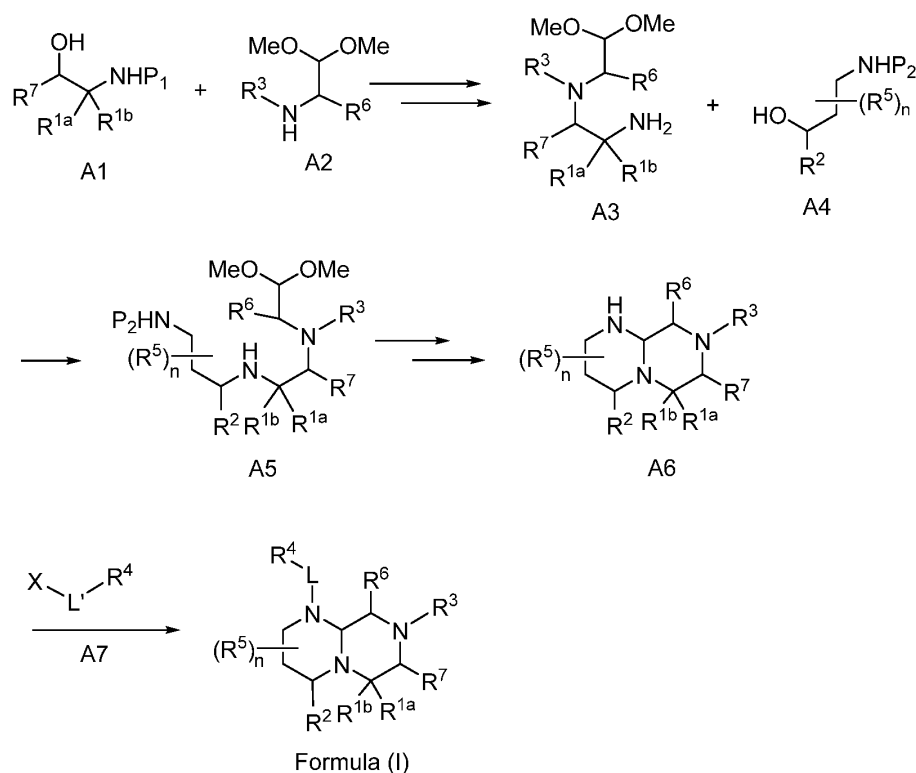
[0104] The Compound A19, and pharmaceutically acceptable salts, isotopic forms, or stereoisomers thereof, including fosgonimeton, may be synthesized and characterized using methods known to those of skill in the art, such as those described in PCT Publication No. WO 2017/210489 A1.

[0105] In some embodiments, fosgonimeton is formulated for subcutaneous administration.

Methods of Synthesis

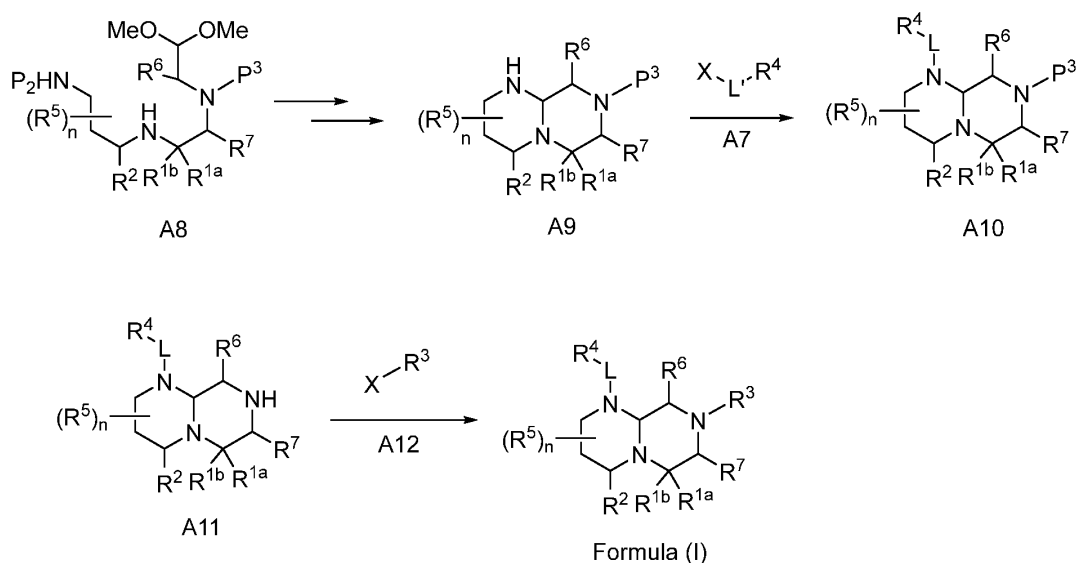
[0106] Compounds of Formula (I), or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, can be prepared by using organic chemistry synthesis methods known in the art. In general, starting components may be obtained from sources such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI, and Fluorochem USA, etc. or synthesized according to sources known to those skilled in the art (see, for example, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* 5th edition (Wiley, December 2000)) or prepared as described herein.

General Reaction Scheme 1.



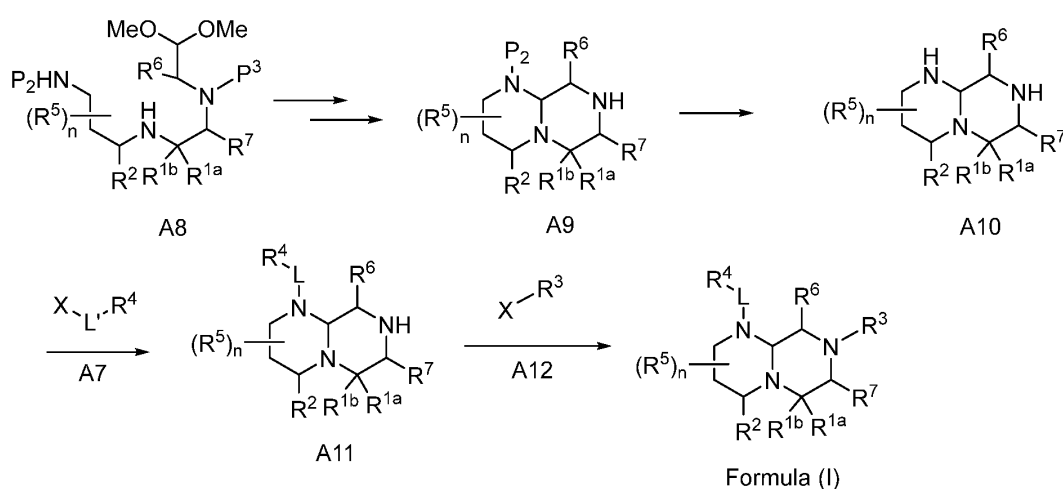
[0107] General Reaction Scheme 1 provides an exemplary method for preparation of compounds of Formula (I). R^{1a}, R^{1b}, R², R³, R⁴, R⁵, R⁶, R⁷, L, and n in General Reaction Scheme 1 are as defined herein. X is a reactive moiety selected to facilitate the desired reaction (*e.g.*, halo). P₁ and P₂ are suitable protecting groups. L' is selected such that a desired L moiety results from the reaction between L'-R⁴ and the secondary amine. Compounds of structure A1 are purchased or prepared according to methods known in the art. Reaction of A1 with A2 under appropriate coupling conditions (*e.g.*, T₃P and base) yields the product of the coupling reaction between A1 and A2, A3. A3 is then reacted with A4 under suitable coupling conditions (*e.g.*, T₃P and base) to afford compound A5. Compound A5 is then cyclized (*e.g.*, using formic acid) and deprotected (*e.g.*, using piperidine) to afford compound A6. Compound A6 is then reacted with compound A7 to afford the final compound of Formula (I) as shown.

General Reaction Scheme 2.



[0108] An alternative method for the synthesis of compounds of Formula (I) is depicted in General Reaction Scheme 2. R^{1a} , R^{1b} , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , L , and n in General Reaction Scheme 2 are as defined herein. P_2 is a suitable protecting group. Each X is a reactive moiety selected to facilitate the desired reaction (*e.g.*, halo). L' is selected such that a desired L moiety results from the reaction between $\text{L}'\text{-R}^4$ and the secondary amine. Intermediate A5 is prepared with a removable protecting group P^3 (*e.g.*, para-methoxybenzyl) as the R^3 group giving intermediate A8. A8 is then cyclized (*e.g.*, using formic acid) and deprotected (*e.g.*, using piperidine) to afford compound A9. Compound A9 is then reacted with A7 to give compound A10. Compound A10 is then deprotected (*e.g.*, with ceric ammonium nitrate) to give compound A11. Compound A11 is then reacted with A12 to provide the final compound of Formula (I).

General Reaction Scheme 3.



[0109] A related method to the one shown in General Reaction Scheme 2 is depicted in General Reaction Scheme 3. In this method, the two amine nitrogen atoms of the bicyclic core are deprotected to provide compound A10, then reacted with A7 to afford compound A11. Subsequent reaction with A12 provides the final compound of Formula (I).

[0110] It should be noted that various alternative strategies for preparation of compounds of Formula (I) are available to those of ordinary skill in the art. For example, other compounds of Formula (I) can be prepared according to analogous methods using the appropriate starting material.

[0111] It will also be appreciated by those skilled in the art that in the processes for preparing the compounds described herein the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups may include hydroxy, amino, and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (for example, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino and amidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl, or arylalkyl esters. Protecting groups are optionally added or removed in accordance with standard techniques, which are known to one skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, *Protective Groups in Organic Synthesis* (1999) 3rd Ed., Wiley. As one of skill in the art would appreciate, the protecting group may also be a polymer resin such as a Wang resin, Rink resin or a 2-chlorotrityl-chloride resin.

Pharmaceutical Compositions and Formulations

[0112] In a further aspect, provided herein are pharmaceutical compositions. The pharmaceutical composition comprises any one (or more) of the foregoing compounds and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated for oral administration. In other embodiments, the pharmaceutical composition is formulated for injection. In still more embodiments, the pharmaceutical compositions comprise a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, and an additional therapeutic agent. Non-limiting examples of such therapeutic agents are described herein below.

[0113] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic,

nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[0114] In certain embodiments, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

[0115] The compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that are used in some embodiments. An exemplary dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[0116] In some embodiments, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, is administered in a single dose. Typically, such administration will be by injection, *e.g.*, intravenous injection, in order to introduce the agent quickly. However, other routes are used as appropriate. A single dose of a compound of the disclosure may also be used for treatment of an acute condition.

[0117] In some embodiments, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, is administered in multiple doses. In some embodiments, dosing is about once, twice, three times, four times, five times, six times, or more than six times per day. In other embodiments, dosing is about once a

month, once every two weeks, once a week, or once every other day. In another embodiment a compound of Formula (I), or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, and another therapeutic agent are administered together about once per day to about 6 times per day. In another embodiment the administration of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, and a therapeutic agent continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[0118] Administration of the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, may continue as long as necessary. In some embodiments, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, is administered chronically on an ongoing basis, *e.g.*, for the treatment of chronic effects (*e.g.*, peripheral or systemic inflammatory conditions).

[0119] In some embodiments, the compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, is administered in dosages. It is known in the art that due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy. Dosing for a compound may be found by routine experimentation in light of the instant disclosure.

[0120] In some embodiments, the compounds Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack

Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999).

[0121] Provided herein are pharmaceutical compositions comprising a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, and a pharmaceutically acceptable diluent(s), excipient(s), or carrier(s). Also provided herein are methods for administering a pharmaceutical composition comprising a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, and a pharmaceutically acceptable diluent(s), excipient(s), or carrier(s).

[0122] In certain embodiments, the compounds are administered as pharmaceutical compositions in which compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are mixed with other therapeutic agents, as in combination therapy. Encompassed herein are all combinations of active ingredients set forth in the methods section below and throughout this disclosure. In specific embodiments, the pharmaceutical compositions include one or more compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

[0123] A pharmaceutical composition, as used herein, refers to a mixture of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, provided herein are administered in a pharmaceutical composition to a mammal having a disease, disorder or medical condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments, therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds described herein are used singly or in combination with one or more therapeutic agents as components of mixtures.

[0124] In one embodiment, one or more compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated in an aqueous solution. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, one or more compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated (*e.g.*, the blood-brain barrier). In still other embodiments wherein the compounds described herein are formulated for other parenteral injections, appropriate formulations include aqueous or non-aqueous solutions. In specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

[0125] In another embodiment, compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated for oral administration. Compounds are formulated by combining the active compounds with, *e.g.*, pharmaceutically acceptable carriers or excipients. In various embodiments, the compounds Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions, and the like.

[0126] In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipients with one or more of the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0127] In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, Carbopol® gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

[0128] In certain embodiments, therapeutically effective amounts of at least one of the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more fillers. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules contain one or more active compounds that is/are dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

[0129] In other embodiments, therapeutically effective amounts of at least one of the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, described herein are formulated for buccal or sublingual administration. Formulations suitable for buccal or sublingual administration include, by way of example only, tablets, lozenges, or gels. In still other embodiments, the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated for parental injection, including formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage forms (*e.g.*, in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical compositions are formulated in a form suitable for parenteral injection as sterile suspensions, solutions or emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral

administration include aqueous solutions of the active compounds in water-soluble form. In additional embodiments, a suspension of an active compound or compounds (*e.g.*, compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof,) are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0130] In still other embodiments, the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are administered topically. The compounds are formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams, or ointments. Such pharmaceutical compositions optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers, and preservatives.

[0131] In yet other embodiments, the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated for transdermal administration. In specific embodiments, transdermal formulations employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. In various embodiments, such patches are constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. In additional embodiments, the transdermal delivery of the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, is accomplished by means of iontophoretic patches and the like. In certain embodiments, transdermal patches provide controlled delivery of the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In specific embodiments, the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. In alternative embodiments, absorption enhancers are used to increase absorption. Absorption

enhancers or carriers include absorbable pharmaceutically acceptable solvents that assist passage through the skin. For example, in one embodiment, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[0132] In other embodiments, the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated for administration by inhalation. Various forms suitable for administration by inhalation include, but are not limited to, aerosols, mists, or powders. Pharmaceutical compositions of any of the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas). In specific embodiments, the dosage unit of a pressurized aerosol is determined by providing a valve to deliver a metered amount. In certain embodiments, capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator is formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0133] In still other embodiments, the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[0134] In certain embodiments, pharmaceutical compositions are formulated in any conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are optionally used as suitable. Pharmaceutical compositions comprising a compound of

Formula (I), or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0135] Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent, or excipient and at least one compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, described herein as an active ingredient. The active ingredient is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of N-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, encompass unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

[0136] Methods for the preparation of compositions comprising the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. Semi-solid compositions include, but are not limited to, gels, suspensions, and creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain

minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[0137] In some embodiments, pharmaceutical compositions comprising at least one compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, illustratively takes the form of a liquid where the agents are present in solution, in suspension or both. Typically, when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

[0138] In certain embodiments, useful aqueous suspensions contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers, *e.g.*, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected, for example, from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate, and dextran.

[0139] Useful pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, *e.g.*, polyethylene glycol 400, and glycol ethers.

[0140] Furthermore, useful pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases, and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[0141] Additionally, useful compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite, and ammonium sulfate.

[0142] Other useful pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide, and cetylpyridinium chloride.

[0143] Still other useful compositions include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, *e.g.*, polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, *e.g.*, octoxynol 10 and octoxynol 40.

[0144] Still other useful compositions include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

[0145] In certain embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

[0146] In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or carriers useful herein. In certain embodiments, organic solvents such as N-methylpyrrolidone are also employed. In additional embodiments, the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are useful herein. In some embodiments, sustained-release capsules release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

[0147] In certain embodiments, the formulations described herein comprise one or more antioxidants, metal chelating agents, thiol containing compounds and/or other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

[0148] In some embodiments, the concentration of the compound of Formula (I) or Compound A19 provided in the pharmaceutical compositions of the present disclosure is less than 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v or v/v.

[0149] In some embodiments, the concentration of the compound of Formula (I) or Compound A19 provided in the pharmaceutical compositions of the present disclosure is greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25%, 19%, 18.75%, 18.50%, 18.25%, 18%, 17.75%, 17.50%, 17.25%, 17%, 16.75%, 16.50%, 16.25%, 16%, 15.75%, 15.50%, 15.25%, 15%, 14.75%, 14.50%, 14.25%, 14%, 13.75%, 13.50%, 13.25%, 13%, 12.75%, 12.50%, 12.25%, 12%, 11.75%, 11.50%, 11.25%, 11%, 10.75%, 10.50%, 10.25%, 10%, 9.75%, 9.50%, 9.25%, 9%, 8.75%, 8.50%, 8.25%, 8%, 7.75%, 7.50%, 7.25%, 7%, 6.75%, 6.50%, 6.25%, 6%, 5.75%, 5.50%, 5.25%, 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 1.25%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v, or v/v.

[0150] In some embodiments, the concentration of the compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, provided in the pharmaceutical compositions ranges from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40 %, approximately 0.01% to

approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, or approximately 1% to approximately 10% w/w, w/v or v/v.

[0151] In some embodiments, the concentration of the compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, provided in the pharmaceutical compositions ranges from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, or approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

[0152] In some embodiments, the amount the compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, provided in the pharmaceutical compositions is equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

[0153] In some embodiments, the amount of the compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, provided in the pharmaceutical compositions of the present disclosure is more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g,

0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, , 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5 g, 3 g, 3.5 g, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5g, 7 g, 7.5g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

[0154] In some embodiments, the amount of the compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, provided in the pharmaceutical compositions ranges from 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

[0155] In some embodiments, the method includes administering Compound A19 or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof by subcutaneous injection.

[0156] In some embodiments, the method includes administering the HGF/MET positive modulator by oral dosage form.

[0157] In some embodiments, the method includes administering Compound **2a** or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof by oral dosage form.

[0158] In some embodiments, the method includes administering Compound **1a** or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof by oral dosage form.

[0159] In some embodiments, the method includes administering Compound **5a** or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof by oral dosage form.

[0160] In some embodiments, the method includes administering Compound **6a** or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof by oral dosage form.

[0161] In some embodiments, the method includes administering Compound **7a** or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof by oral dosage form.

Kits/Articles of Manufacture

[0162] For use in the therapeutic applications described herein, kits and articles of manufacture are also provided. In some embodiments, such kits comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers are formed from a variety of materials such as glass or plastic.

[0163] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include those found in, *e.g.*, U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. For example, the container(s) includes one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprise a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[0164] For example, a kit typically includes one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound of Formula (I), or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes, carriers, packages, containers, vials, and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included. A label is optionally on or associated with the container. For example, a label is on a container when letters, numbers or other characters forming the label are attached, molded, or etched into the container itself, or a label is associated with a container when it is present within a receptacle or carrier that also holds the container, *e.g.*, as a package insert. In addition, a label is used to indicate that the contents are to be used for a specific therapeutic application. In addition, the label indicates directions for use of the contents, such as in the methods described herein. In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack for example contains metal or plastic foil, such as a blister pack. A pack or dispenser device may be accompanied by instructions for administration. A pack or dispenser may be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions containing a compound of Formula (I), or a

pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, formulated in a compatible pharmaceutical carrier are prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Methods of Use/Treatments

[0165] Embodiments of the present disclosure provide a method for modulating hepatocyte growth factor in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound as disclosed herein (*e.g.*, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof). In some embodiments, a compound described herein activates hepatocyte growth factor. In some embodiments, a compound as described herein positively modulates hepatocyte growth factor activity. Modulation (*e.g.*, inhibition or activation) of hepatocyte growth factor can be assessed and demonstrated by a wide variety of ways known in the art. Kits and commercially available assays can be utilized for determining whether and to what degree hepatocyte growth factor has been modulated (*e.g.*, inhibited or activated).

[0166] In some embodiments, provided herein are compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, for use in positively modulating hepatocyte growth factor in a subject in need thereof. In some embodiments, provided herein are compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, for the manufacture of a medicament for modulating hepatocyte growth factor in a subject in need thereof.

[0167] Applicant has discovered that the compounds of Formula (I) or Compound A19 show promising activity related to certain diseases of interest. Accordingly, in one aspect, provided herein is a method for modulating hepatocyte growth factor in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, provided herein is a method for activating hepatocyte growth factor in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, provided herein is a method for positively modulating hepatocyte growth factor activity in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

[0168] In certain more specific embodiments, the positive modulation comprises treating, or reducing the symptoms of, a disease, condition, or injury. In some embodiments, the disease, condition, or injury is a peripheral and/or systemic inflammatory condition. The peripheral and/or systemic inflammatory condition may be gastrointestinal, dermatological, ophthalmological, related to metabolic diseases, or pulmonological.

[0169] In some embodiments, the peripheral and/or systemic inflammatory condition may be inflammatory bowel disease, Crohn's disease, ulcerative colitis, coeliac disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, dermatomyositis, polymyositis, noninfectious uveitis, optic neuritis, Leber hereditary optic neuropathy (LHON), macular degeneration, retinal degeneration, myasthenia gravis, type 2 diabetes, obesity, coronary heart disease, gout, fatty liver disease, seasonal allergies, chronic obstructive pulmonary disease (COPD), or endometriosis.

[0170] In some embodiments, provided herein are methods of treating inflammatory bowel disease, Crohn's disease, ulcerative colitis, coeliac disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, dermatomyositis, polymyositis, noninfectious uveitis, optic neuritis, Leber hereditary optic neuropathy (LHON), macular degeneration, retinal degeneration, myasthenia gravis, type 2 diabetes, obesity, coronary heart disease, gout, fatty liver disease, seasonal allergies, chronic obstructive pulmonary disease (COPD), or endometriosis in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0171] In some embodiments, provided herein are methods of treating inflammatory bowel disease in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0172] In some embodiments, provided herein are methods of treating Crohn's disease in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0173] In some embodiments, provided herein are methods of treating ulcerative colitis in a subject. The method includes administering an effective amount of a compound in Table 1, a

compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0174] In some embodiments, provided herein are methods of treating coeliac disease in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0175] In some embodiments, provided herein are methods of treating rheumatoid arthritis in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0176] In some embodiments, provided herein are methods of treating psoriasis in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0177] In some embodiments, provided herein are methods of treating noninfectious uveitis in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0178] In some embodiments, provided herein are methods of treating type 2 diabetes in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0179] In some embodiments, provided herein are methods of treating obesity in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0180] In some embodiments, provided herein are methods of treating coronary heart disease in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0181] In some embodiments, provided herein are methods of treating gout in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0182] In some embodiments, provided herein are methods of treating fatty liver disease in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0183] In some embodiments, provided herein are methods of treating seasonal allergies in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0184] In some embodiments, provided herein are methods of treating COPD in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0185] In some embodiments, provided herein are methods of treating endometriosis in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0186] In some embodiments, provided herein are methods of treating systemic lupus erythematosus in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0187] In some embodiments, provided herein are methods of treating dermatomyositis in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0188] In some embodiments, provided herein are methods of treating polymyositis in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0189] In some embodiments, provided herein are methods of treating optic neuritis in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0190] In some embodiments, provided herein are methods of treating LHON in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0191] In some embodiments, provided herein are methods of treating macular degeneration in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0192] In some embodiments, provided herein are methods of treating retinal degeneration in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0193] In some embodiments, provided herein are methods of treating myasthenia gravis in a subject. The method includes administering an effective amount of a compound in Table 1, a compound in Table 1a, Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0194] In some embodiments, provided herein are methods of treating inflammatory bowel disease, Crohn's disease, ulcerative colitis, coeliac disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, dermatomyositis, polymyositis, noninfectious uveitis, optic neuritis, leber hereditary optic neuropathy (LHON), macular degeneration, retinal degeneration, myasthenia gravis, type 2 diabetes, obesity, coronary heart disease, gout, fatty liver disease, seasonal allergies, chronic obstructive pulmonary disease (COPD), or endometriosis in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0195] In some embodiments, provided herein are methods of treating inflammatory bowel disease in a subject. The method includes administering an effective amount of Compound **1a**,

Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0196] In some embodiments, provided herein are methods of treating Crohn's disease in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0197] In some embodiments, provided herein are methods of treating ulcerative colitis in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0198] In some embodiments, provided herein are methods of treating coeliac disease in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0199] In some embodiments, provided herein are methods of treating rheumatoid arthritis in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0200] In some embodiments, provided herein are methods of treating psoriasis in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0201] In some embodiments, provided herein are methods of treating noninfectious uveitis in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0202] In some embodiments, provided herein are methods of treating type 2 diabetes in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0203] In some embodiments, provided herein are methods of treating obesity in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0204] In some embodiments, provided herein are methods of treating coronary heart disease in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0205] In some embodiments, provided herein are methods of treating gout in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0206] In some embodiments, provided herein are methods of treating fatty liver disease in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0207] In some embodiments, provided herein are methods of treating seasonal allergies in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0208] In some embodiments, provided herein are methods of treating COPD in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0209] In some embodiments, provided herein are methods of treating endometriosis in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0210] In some embodiments, provided herein are methods of treating systemic lupus erythematosus in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0211] In some embodiments, provided herein are methods of treating dermatomyositis in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0212] In some embodiments, provided herein are methods of treating polymyositis in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0213] In some embodiments, provided herein are methods of treating optic neuritis in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0214] In some embodiments, provided herein are methods of treating LHON in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0215] In some embodiments, provided herein are methods of treating macular degeneration in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0216] In some embodiments, provided herein are methods of treating retinal degeneration in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0217] In some embodiments, provided herein are methods of treating myasthenia gravis in a subject. The method includes administering an effective amount of Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof to the subject.

[0218] In some embodiments, the peripheral and/or systemic inflammatory condition is not caused by neuroinflammation or a disease or disorder of the central nervous system. In some embodiments, the peripheral and/or systemic inflammatory condition is not caused by a dementia. In some embodiments, the peripheral and/or systemic inflammatory condition is not

caused by a neurodegenerative disease. In some embodiments, the peripheral and/or systemic inflammatory condition is not caused by Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, traumatic brain injury, or sensorineural hearing and vision loss. In some embodiments, the subject being treated for the peripheral and/or systemic inflammatory condition is not suffering from a dementia. In some embodiments, the subject being treated for the peripheral and/or systemic inflammatory condition is not suffering from a neurodegenerative disease. In some embodiments, the subject being treated for the peripheral and/or systemic inflammatory condition is not suffering from Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, traumatic brain injury, and/or sensorineural hearing and vision loss.

[0219] In some embodiments, the peripheral and/or systemic inflammatory condition is not associated with neuroinflammation or a disease or disorder of the central nervous system. In some embodiments, the peripheral and/or systemic inflammatory condition is not associated with a dementia. In some embodiments, the peripheral and/or systemic inflammatory condition is not associated with a neurodegenerative disease. In some embodiments, the peripheral and/or systemic inflammatory condition is not associated with Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, traumatic brain injury, or sensorineural hearing and vision loss. In some embodiments, the subject being treated for peripheral and/or systemic inflammatory condition is not suffering from a dementia.

[0220] In some embodiments, the disclosure provides methods of modulating protein activity (*e.g.*, hepatocyte growth factor activity) in a subject including but not limited to rodents and mammal (*e.g.*, human) by administering into the subject an effective amount of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, modulation of hepatocyte growth factor is activation of hepatocyte growth factor. In some embodiments, the percentage modulation exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%. In some embodiments, the percentage of inhibiting exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.

[0221] In some embodiments, the disclosure provides methods of modulating hepatocyte growth factor activity in a cell by contacting said cell with an amount of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, sufficient to modulate the activity of hepatocyte growth factor. In some

embodiments, the disclosure provides methods of modulating hepatocyte growth factor activity in a tissue by contacting said tissue with an amount of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, sufficient to modulate the activity of hepatocyte growth factor in the tissue. In some embodiments, the disclosure provides methods of modulating hepatocyte growth factor activity in an organism by contacting said organism with an amount of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, sufficient to modulate the activity of hepatocyte growth factor in the organism. In some embodiments, the disclosure provides methods of modulating hepatocyte growth factor activity in an animal by contacting the animal with an amount of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, sufficient to modulate the activity of hepatocyte growth factor in the animal. In some embodiments, the disclosure provides methods of modulating hepatocyte growth factor activity in a mammal by contacting the mammal with an amount of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, sufficient to modulate the activity of hepatocyte growth factor in the mammal. In some embodiments, the disclosure provides methods of modulating hepatocyte growth factor activity in a human by contacting the human with an amount of a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, sufficient to modulate the activity of hepatocyte growth factor in the human. In other embodiments, the present disclosure provides methods of treating a disease mediated by hepatocyte growth factor activity in a subject in need of such treatment. In some variations, modulation of hepatocyte growth factor by a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, involves activation of hepatocyte growth factor.

[0222] In some embodiments, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level in the subject of at least one proinflammatory molecule. In some embodiments, the compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level of at least one proinflammatory molecule selected G-CSF, CCL3, CXCL1, CXCL2, CXCL10, IL-1 α , IL-1 β , IL-4, IL-10, IL-12p70, IL-17A, TNF α , and IFN γ . In some embodiments, the compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level of at least one proinflammatory molecule selected from IL-1 β , IL-4, IL-6, TNF- α , and IFN γ . In

some embodiments, the compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level of at least one proinflammatory molecule selected from BAFF, G-CSF, ENA-78 (CXCL5), Eotaxin (CCL11), IL-2R, LIF, MIP-1Beta (CCL4) and MIP-1Alpha (CCL3).

[0223] In some embodiments, a compound of Table 1, Table 1A or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level in the subject of at least one proinflammatory molecule. In some embodiments, the compound of Table 1, Table 1A or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level of at least one proinflammatory molecule selected G-CSF, CCL3, CXCL1, CXCL2, CXCL10, IL-1 α , IL-1 β , IL-4, IL-10, IL-12p70, IL-17A, TNF α , and IFN γ . In some embodiments, the compound of Table 1, Table 1A or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level of at least one proinflammatory molecule selected from IL-1 β , IL-4, IL-6, TNF- α , and IFN γ . In some embodiments, the compound of Table 1, Table 1A or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level of at least one proinflammatory molecule selected from BAFF, G-CSF, ENA-78 (CXCL5), Eotaxin (CCL11), IL-2R, LIF, MIP-1Beta (CCL4) and MIP-1Alpha (CCL3).

[0224] In some embodiments, Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level in the subject of at least one proinflammatory molecule. In some embodiments, Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level of at least one proinflammatory molecule selected G-CSF, CCL3, CXCL1, CXCL2, CXCL10, IL-1 α , IL-1 β , IL-4, IL-10, IL-12p70, IL-17A, TNF α , and IFN γ . In some embodiments, Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level of at least one proinflammatory molecule selected from IL-1 β , IL-4, IL-6, TNF- α , and IFN γ . In some embodiments, Compound **1a**, Compound **2a**, Compound **5a**, Compound **6a**, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof decreases the level of at least one

proinflammatory molecule selected from BAFF, G-CSF, ENA-78 (CXCL5), Eotaxin (CCL11), IL-2R, LIF, MIP-1Beta (CCL4) and MIP-1Alpha (CCL3).

[0225] Other embodiments provide methods for combination therapies in which a therapeutic agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In one aspect, such therapy includes but is not limited to the combination of one or more compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, with therapeutic agents, therapeutic antibodies, and other forms of treatment, to provide a synergistic or additive therapeutic effect.

[0226] Many therapeutic agents are presently known in the art and can be used in combination with the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof. In some embodiments, a subject having a peripheral and/or systemic inflammatory condition is also treated with another anti-inflammatory agent, such as a steroid.

[0227] In some embodiments, the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are formulated or administered in conjunction with liquid or solid tissue barriers also known as lubricants. Examples of tissue barriers include, but are not limited to, polysaccharides, polyglycans, seprafilm®, and hyaluronic acid.

[0228] Further therapeutic agents that can be combined with a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are found in Goodman and Gilman's "The Pharmacological Basis of Therapeutics" Tenth Edition edited by Hardman, Limbird and Gilman or the Physician's Desk Reference, both of which are incorporated herein by reference in their entirety.

[0229] The compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, can be used in combination with the therapeutic agents disclosed herein depending on the condition being treated. Hence, in some embodiments the one or more compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, will be co-administered with other therapeutic agents as described above. When used in combination therapy, the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable

salt, isotopic form, or stereoisomer thereof, are administered with the second therapeutic agent simultaneously or separately. This administration in combination can include simultaneous administration in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, and any of the therapeutic agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, and any of the therapeutic agents described above can be simultaneously administered, wherein both are present in separate formulations. In another alternative, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, can be administered just followed by and any of the therapeutic agents described above, or vice versa. In some embodiments of the separate administration protocol, a compound of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, and any of the therapeutic agents described above are administered a few minutes apart, or a few hours apart, or a few days apart.

[0230] The examples and preparations provided below further illustrate and exemplify the compounds of Formula (I) or Compound A19, or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, and methods of preparing such compounds. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples and preparations. In the following examples, and throughout the specification and claims, molecules with a single stereocenter, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more stereocenters, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

EXAMPLES

[0231] The following examples are provided for exemplary purposes. Methods for preparation of compounds of Formula (I), or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, are provided in PCT Publication WO2022/094400, which is incorporated herein by reference, or can be derived by one of ordinary skill in the art.

Example B1: Reduction of inflammatory pain-related behaviors and inflammation biomarkers following treatment in a rodent CFA inflammatory pain model

[0232] Response to peripheral inflammatory stimulus can be modeled by administering complete Freund's adjuvant (CFA), a suspension of desiccated mycobacterium in paraffin oil and mannide monooleate, by subcutaneous injection into the rat's footpad. The introduction of CFA to peripheral tissues leads to a rapid, sustained, inflammatory reaction in the exposed tissue within 24 hours. Subcutaneous administration of CFA in the plantar region of the paw induces inflammatory pain-related behaviors that persist for at least 8 days. CFA treatment also leads to the accumulation of inflammatory cytokines in paw tissue at the site of injury. The extent of inflammatory response to CFA can be assessed by quantification of inflammatory cytokines in paw skin homogenate, and inflammatory pain-related behaviors by tests of mechanical allodynia (von Frey test) and thermal hyperalgesia (Hargreaves test).

[0233] In one study, Compound 2a was tested for its ability to reduce inflammatory pain-related behaviors in the CFA inflammation model. On study day 0, 50 µg of CFA was administered subcutaneously in the plantar of the right hind paw. Animals were treated daily with Compound 2a in solution via oral gavage (PO) at doses of 1, 0.1, and 0.025 mg/kg. Treatment began before CFA injection on study day -1 and continued through study day 8.

[0234] Mechanical allodynia was measured using the von Frey test. In this test, rats were placed on a wire mesh and a series of filaments designed to deliver a probing force ranging from 4 to 26 grams were applied to the mid-plantar surface of the right hind paw. Animals indicated pain response by lifting the probed paw. The minimal force required to elicit the withdrawal response was recorded as the paw withdrawal threshold (PWT). Von Frey testing was performed 1 hour after Compound 2a dosing on study day 1, 3, and 7, and was also tested pre-dosing on day 7. Statistical analysis was performed using a 1-way ANOVA with Tukey post-test. A p-value below 0.05 was considered statistically significant. Results are summarized in Table 2. Control animals stimulated with CFA but treated with only vehicle had high sensitivity to mechanical stimulation compared to normal control animals. Treatment with Compound 2a at a dose of 1 mg/kg resulted in reduced mechanical allodynia on study day 7 in the post-dose testing.

[0235] Thermal hyperalgesia was measured using the Hargreaves method. A temperature ramp was applied to the right hind paw via a directed light beam and the paw withdrawal latency (PWL) was recorded as a measure of sensitivity to thermal stimulation. One hour post-dose testing was performed on study days 1, 3, and 7, and pre-dose testing was performed on day 7. Statistical analysis was performed using a 1-way ANOVA with Tukey post-test. A p-value below 0.05 was considered statistically significant. Results are summarized in Table 2.

Control animals stimulated with CFA but treated with only vehicle had a high sensitivity to thermal stimulation compared to normal control animals. Treatment with Compound 2a at a dose of 1 mg/kg resulted in reduced thermal sensitivity on day 3 and in pre-dose testing on day 7.

Table 2. Mechanical allodynia and thermal hyperalgesia in response to CFA-based inflammatory pain stimulation are reduced by Compound 2a.

		Compound 2a		
	Dose (mg/kg, PO)	1	0.1	0.025
Mechanical Allodynia	Day 1	NS	NS	NS
	Day 3	NS	NS	NS
	Day 7 pre-dose	NS	NS	NS
	Day 7 post-dose	+	NS	NS
Thermal Hyperalgesia	Day 1	NS	NS	NS
	Day 3	+	NS	NS
	Day 7 pre-dose	+	NS	NS
	Day 7 post-dose	NS	NS	NS

NS = no statistically significant change in sensitivity compared to CFA alone

+ = statistically significant change in sensitivity compared to CFA alone, $p < 0.05$

[0236] In another study, Compounds 1a, 5a, and 6a were similarly tested against CFA-induced inflammatory stimulation in the right hind foot for their ability to reduce pain-related behaviors. This study also included quantification of inflammatory cytokine expression in paw skin homogenate. Inflammatory pain stimulation with CFA injection and assessment of mechanical and thermal pain-related behaviors were performed as described above.

[0237] Intraplantar CFA injection occurred at day 0. Treatment with Compounds 1a, 5a, and 6a occurred daily from day -1 to day 8. At day 8, the rats were terminated and cytokine levels were measured in paw skin. Tissue from paw bone, joint, and muscle were obtained for H&E staining and analysis. Cytokine levels in CFA-stimulated test compound-treated animals were compared to CFA-stimulated vehicle-treated animals. Analytes included interleukin 4 (IL-4), tumor necrosis factor alpha (TNF- α) and interferon gamma (IFN- γ) Statistical analysis consisted of 1-way ANOVA followed by Dunnett's multiple comparisons post-test. Mechanical allodynia and thermal hyperalgesia were tested 1-hour post-dosing on days 1, 3, and 7. PWT

refers to lower paw withdrawal threshold where a higher value corresponds to a higher pain threshold. PWL refers to lower paw withdrawal latency where a higher value corresponds to a higher pain threshold.

[0238] As shown in Table 3, Compound 1a significantly reduced sensitivity to mechanical stimulation on study days 1, 3, and 7, and similarly reduced thermal sensitivity on study days 1, 3, and 7. Treatment with compound 5a reduced mechanical sensitivity on study day 1 and reduced thermal sensitivity on study days 1 and 7. Compound 6a reduced thermal sensitivity on study day 7.

Table 3. Significant reduction in mechanical and thermal pain behaviors

		Compound 1a		Compound 5a		Compound 6a	
	Dose (mg/kg, PO)	8	16	10	20	2.5	10
Mechanical Allodynia	Day 1	+	+	+	+	NS	NS
	Day 3	+	+	NS	NS	NS	NS
	Day 7	NS	+	NS	NS	NS	NS
Thermal Hyperalgesia	Day 1	NS	+	+	NS	NS	NS
	Day 3	NS	+	NS	NS	NS	NS
	Day 7	+	+	+	+	+	+

NS = no statistically significant change in sensitivity compared to CFA alone

+ = statistically significant change in sensitivity compared to CFA alone, $p < 0.05$

[0239] Compounds 1a and 5a showed a statistically significant increase in PWT on day 1 and Compound 1a showed a statistically significant increase in PWT on day 3 (8 and 16 mg/kg) and 7 (16 mg/kg) (Table 3 and data not shown).

[0240] Compounds 1a, 5a, and 6a showed a statistically significant increase in PWL on day 7 at each dose (Table 3 and data not shown).

[0241] On day 5, mechanical allodynia and thermal hyperalgesia were assessed at 1 hour pre-dosing. On Day 5, threshold levels for each of the compounds were tested. Compounds 1a and 6a both showed a statistically significant increase in PWL (data not shown).

[0242] Treatment had no significant effect on paw thickness despite observable pain attenuation (data not shown). A significant reduction in IL-4, TNF- α , and IFN- γ was detected in paw skin at day 8 of the study (Table 4 and data not shown).

[0243] All test compounds reduced the expression of the assessed cytokines in at least one tested dose, except for compound 6a which had no effect on IFN- γ expression (Table 4). These results suggest that the test compounds produce a meaningful anti-inflammatory effect in response to CFA-stimulated peripheral inflammation.

Table 4. Cytokine expression quantification in the paw skin of CFA-stimulated animals treated with the indicated test compounds

		Compound 1a		Compound 5a		Compound 6a	
	Dose (mg/kg, PO)	8	16	10	20	2.5	10
Cytokine analyte	IL-4	+	+	+	+	+	NS
	TNF- α	+	+	+	+	+	NS
	IFN- γ	+	NS	+	+	NS	NS

NS = no statistically significant change in expression compared to CFA alone

+ = statistically significant change in expression compared to CFA alone, $p < 0.05$

Example B2: Reduction of inflammation following pulmonary LPS challenge.

[0244] Acute pulmonary inflammation can be effectively modeled in rats by intratracheal administration of bacterial lipopolysaccharides (LPS). The severity of inflammatory response can be measured by quantifying the amount of immune cell infiltration and secretion of cytokine signaling proteins in bronchoalveolar lavage fluid (BALF). Activation of the HGF/MET signaling system by HGF/MET positive modulators is expected to reduce the inflammatory response. Two test compounds, Compound 1a and Compound 5a, were evaluated for their ability to reduce acute pulmonary inflammation in an intranasal LPS model.

[0245] In this study, acute pulmonary inflammation was induced in healthy male Sprague-Dawley rats (7-9 weeks old at study start) by intratracheal instillation of 20 μ g LPS in saline. Test animals were treated with test compounds twice, at 24 hours and 0.5 hours, before LPS treatment by intravenous (IV) injection. The anti-inflammatory corticosteroid Dexamethasone (Dex) was used as a positive control and was administered 1 hour before LPS treatment by intraperitoneal (IP) injection at 3 mg/kg. Four hours post-LPS administration, animals were euthanized by intraperitoneal injection of thiopentone and 20 mL of cold Hanks Balanced Salt

Solution, pH 7.2, was infused into the lungs through tracheal cannulation. BALF was then collected.

[0246] Immune cell infiltration in BALF was quantified as an assessment of an inflammatory response, with the results shown in Table 5. Immune cell infiltration was performed by counting total leukocytes using a MUSE® mini flow cytometer, and by manual counting of neutrophil cells in cytospin smears stained with Leishman's staining reagent. Treatment with Compound 1a and Compound 5a reduced both total leukocyte counts and neutrophil counts compared to LPS-only controls.

Table 5. Immune cell infiltration in BALF from pulmonary LPS-stimulated rats

	Dex	Compound 1a			Compound 5a		
Dose (mg/kg)	3	0.75	0.075	0.0075	7.5	0.75	0.075
Total Leukocytes	+++	NS	+	++	+	+	++
Neutrophils	+++	NS	+	++	+	+	++

NS means not significant

+ = >5% reduction in cell count vs disease control

++ = >25% reduction in cell count vs disease control

+++ = >75% reduction in cell count vs disease control

[0247] Cytokine expression in BALF supernatant was quantified by multiplex immunoassay using a MAGPIX multiplexing unit with a cytokine multiplex kit (Merck-Millipore, Cat# RECYMAG65K27PMX). The panel of tested cytokines included growth factors (G-CSF, GM-CSF, EGF, VEGF, TNF- α), chemokines (CCL2, CCL3, CCL5, CCL11, CXCL 1, CXCL 2, CXCL5, CXCL10, CX3CL1), interleukins (IL-1 α , IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-13, IL-17A), and interferon gamma (IFN γ). The results of this analysis are shown in Table 6. Statistically significant change from LPS-only animals was determined by Student's T-test, with $p < 0.05$ indicating statistically significant change in cytokine expression levels. Treatment with Compound 1a lead to significant changes in expression of G-CSF, CXCL2, CXCL10, IFN- γ , and IL-1 β . Treatment with Compound 5a led to significant changes in expression of CCL3, CXCL1, IFN- γ , IL-1 α , IL-1 β , IL-10, IL-12p70, and IL-17A. These results indicate that treatment with test compounds had a meaningful impact on acute pulmonary inflammation response to LPS by decreasing the levels of proinflammatory molecules. The normal process of inflammation is regulated and promoted by expression, secretion, and

distribution of inflammatory signaling proteins. Therapeutics intended to reduce inflammation are commonly identified by their ability to change the expression levels of inflammatory signaling molecules, either by disruption of the inflammatory pathway directly, or resolution of the inflammatory signaling cascade. The compounds provided herein are expected to be capable of interrupting inflammatory signaling based on their demonstrated impact on the expression of noteworthy inflammatory cytokines.

Table 6. Significant change in cytokine expression in BALF supernatant from pulmonary LPS-stimulated rats

		Dex	Compound 1a			Compound 5a		
Dose (mg/kg)		3	0.75	0.075	0.0075	7.5	0.75	0.075
Growth Factors	G-CSF	+	+					
	GM-CSF							
	EGF	+						+
	VEGF							
	TNF- α	+						
Chemokines	CCL2	+						
	CCL3	+						+
	CCL5	+						
	CCL11	+						
	CXCL1	+						
	CXCL2		+					
	CXCL5	+						
	CXCL10	+	+		+			
	CX3CL1	+						+
	IFN- γ	+			+		+	+
Interleukins	IL-1 α	+				+	+	+

IL-1 β	+	+				+	+
IL-2							
IL-4							
IL-5	+						
IL-6	+						
IL-10	+				+	+	+
IL-12p70	+						+
IL-13	+						
IL-17A	+					+	+

+ = Significant change in cytokine quantification, $p < 0.05$ by Student's T-test; a blank cell indicates that results were not statistically significant.

Example B3: Reduction of pro-inflammatory cytokine expression in macrophage-like cell cultures.

[0248] Inflammation plays a crucial role in disease progression and is a complex phenomenon involving various cells that affect many extra- and intracellular signaling pathways and cytokine production. Macrophages are tissue-resident or infiltrated immune cells critical for innate immunity, normal tissue development, homeostasis, and repair of damaged tissue. Activated macrophages participate in developing systemic and peripheral inflammation, responding to toxic exogenous substances (like LPS) or endogenous substances. Here, we use THP-1 cells as an in-vitro cell model to evaluate mechanisms relevant to systemic and peripheral inflammation. Differentiation with PMA causes THP-1 monocyte cells to acquire functional and morphological resemblance to macrophages. LPS interacts with THP-1 differentiated macrophage through the toll-like receptor 4, triggering the inflammatory response and stimulating pro-inflammatory cytokine release and eventually leading to cellular death. Here we investigated whether test compounds have anti-inflammatory effects on LPS-challenged macrophage cultures. THP-1-differentiated macrophages were treated with test compounds for 20 minutes, followed by 24 hrs of LPS challenge. Culture supernatants were then collected and analyzed for the presence of pro-inflammatory cytokines: interleukin 1 β (IL-1 β), interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α).

[0249] Cytokine quantification in cell culture supernatants was accomplished by homogeneous time-resolved fluorescence (HTRF) kits to assess levels of IL-1 β (Human IL-1 β

kit, #62HIL1BPEG, Cisbio) and IL-6 (Human IL-6 kit, 62HIL06PET, Cisbio), and by ELISA to determine the levels of TNF- α (Human TNF- α ELISA kit, KHC3011, ThermoFisher).

[0250] Data analysis was performed via 1-way ANOVA with Tukey post-test compared to LPS treatment cultures using Prism statistical software (GraphPad). Tabular data indicates significance of reduction in culture supernatants for the indicated analyte at the indicated dose.

[0251] The results are shown in Table 7. Treatment with Compounds 1a, 5a, 6a, and A19 active metabolite (ATH-1001) all significantly reduced the expression of IL-1 β and TNF- α at at least one tested dose. Treatment with Compounds 1a, 5a, and A19 active metabolite all significantly reduced the expression of IL-6 at at least one tested dose “NS” indicates a non-significant reduction in the indicated cytokine. “+” indicates a p value < 0.05 in Tukey post test. “++” indicates a p value < 0.01 in Tukey post test.

Table 7: Significant reduction in pro-inflammatory cytokine expression by THP-1 immune cells in vitro

Compound 1a				Compound 5a			
Dose	Inflammatory Analyte			Dose	Inflammatory Analyte		
(nM)	IL-1 β	IL-6	TNF- α	(nM)	IL-1 β	IL-6	TNF- α
0.1	++	NS	++	0.1	++	NS	NS
10	++	++	++	10	++	+	NS
1000	++	+	++	1000	++	++	+

Compound 6a				Compound A19, active metabolite			
Dose	Inflammatory Analyte			Dose	Inflammatory Analyte		
(nM)	IL-1 β	IL-6	TNF- α	(nM)	IL-1 β	IL-6	TNF- α
0.1	NS	NS	NS	0.1	NS	NS	NS
10	NS	NS	NS	10	++	+	+
1000	+	NS	+	1000	+	++	++

Example B4: Reduction in Streptozotocin-Induced Inflammatory Cytokines in Response to Compound Treatment.

[0252] Administration of streptozotocin, a chemotherapeutic agent with specific toxic effects on pancreatic islet cells, produces a profound and systemic inflammatory response in animals.

Streptozotocin enters pancreatic B cells via a glucose transporter, disrupts the function of these cells by cross-linking action in DNA, and produces uncontrolled hyperglycemia. This condition leads to strong, chronic induction of inflammatory pathways, and is a widely utilized model of peripheral inflammation associated with diabetic indications.

[0253] To assess the ability of test compounds to reduce systemic inflammation in the streptozotocin-diabetic model in Sprague Dawley rats, disease was induced by a single intravenous dose of streptozotocin (STZ, 55 mg/kg) on study day 0, and diabetic disease induction was confirmed on day 4 by estimating blood glucose levels. Rats with blood glucose levels above 200 mg/dl were considered successfully induced and included in the study. Treatment with test compounds began on study day 15 and continued with a single dose each day via oral gavage (PO) until study day 28, when blood plasma was collected for cytokine expression analysis.

[0254] Cytokines were quantified using a bead-capture detection system (ProcartaPlex, ThermoFisher, Catalog #: PPX-090MXKA44V) using a Luminex multiplex detection system. Each analyte was quantified in relation to a standard curve and the abundance in plasma was measured in pg/ml. Interferon gamma (IFN- γ) and interleukin-4 (IL-4) were strongly upregulated by STZ stimulation and also reduced in response to test compound treatment. IFN- γ is expressed in response to other inflammatory cytokines and promotes inflammation by activation of the JAK/STAT signaling pathway. IL-4 is a pro-inflammatory cytokine that activates several types of inflammatory macrophage cells. Thus, reduction in the expression of either of these analytes represents a reduction in inflammatory response to disease induction. Statistical analysis was conducted by one-way ANOVA followed by Dunnett's multiple comparisons post-test against untreated disease control.

[0255] Three test compounds were evaluated in this study, Compound 1a, Compound 5a, and Compound 6a. The results are summarized in Table 8. Daily treatment with Compound 1a significantly reduced the expression of both IFN- γ and IL-4 at doses of 8 and 16 mg/kg. Daily treatment with Compound 5a reduced expression of IFN- γ and IL-4 at a dose of 20 mg/kg. Daily treatment with Compound 6a reduced expression of IFN- γ and IL-4 at a dose of 10 mg/kg. These results indicate that the indicated test compounds have the ability to reduce peripheral inflammation resulting from chronic hyperglycemia.

Table 8: Plasma cytokine reduction in STZ-induced rats following daily treatment with the indicated test compounds

Test Compound	Dose	Significant reduction in cytokine expression compared to STZ diseases control	
		IFN- γ	IL-4
1a	8 mg/kg	++	+++
1a	16 mg/kg	++++	++++
5a	20 mg/kg	++++	++++
6a	10 mg/kg	++++	++++

Statistical outliers were identified by ROUT method ($Q = 1\%$) and removed prior to statistical analysis. Statistical analysis consists of one-way ANOVA with Dunnett's multiple comparisons post-test vs untreated STZ disease controls. ++ = $p < 0.01$, +++ = $p < 0.001$, ++++ = $p < 0.0001$

Example B5: Reduction of pro-inflammatory cytokine expression in a mouse model of LPS-induced inflammation.

[0256] Administration of bacterial lipopolysaccharides (LPS) induces an inflammatory response and stimulates pro-inflammatory cytokine release and eventually leads to cellular death. In this study, the ability of Compound A19 to reduce systemic inflammation in an LPS model of inflammation in 8-10 week old male C57B/6N mice was assessed.

[0257] The study design was as follows:

Table 9. LPS induced inflammation study design

Group	Animal ID	Treatment (Day 0-3)		Challenge (T=20 min. following first treatment)	Procedures (challenge; N=8/time-point)
		Test article	Dose level and frequency		
1	1-8	Vehicle control	10 mL/kg SC/QD	WFI 10 mL/kg IP	- T = 72h (20 min. post-last dosing) - Blood for serum/cytokines
2	9-40	Vehicle control	10 mL/kg SC/QD		

3	41-72	AT-08	0.125 mg/kg SC/QD	LPS 5 mg/kg IP	T = 1.5h, 6h, 24h (20 min. post-second dosing) - Blood for serum/cytokines - T = 72h (20 min. post-last dosing) - Blood for serum/compound concentration (groups 3-5) and cytokines (all groups)
4	73-104	AT-08	0.5 mg/kg SC/QD		
5	105-136	AT-08	1.25 mg/kg SC/QD		

IP – intraperitoneal, LPS – lipopolysaccharide, QD – once a day, SC – subcutaneous, WFI – water for injections

[0258] Animals from groups 1 and 2 served as control groups and received vehicle (saline – 0.9% NaCl). Starting from Day (D) 0, animals from both groups were treated once a day (QD) via subcutaneous (SC) route at 10 mL/kg. All animals from group 1 were treated for 4 consecutive days, while the first 16 animals from group 2 received a single dose, the next 8 animals were treated for two consecutive days, and the remaining 8 animals were treated for 4 consecutive days. Prior to dosing, the animals were weighed, and the amount of vehicle administered adjusted according to individual weights.

[0259] The test article, Compound A19, was dissolved in saline (0.9% NaCl), pH 7.4-7.7, and prepared to achieve final concentrations of 0.125, 0.5 and 1.25 mg/kg for groups 3-5, respectively. Starting from D0, animals from groups 3-5 were treated with 0.125, 0.5 or 1.25 mg/kg of Compound A19, respectively, once a day (QD) via subcutaneous (SC) route at 10 mL/kg. The first 16 animals from each group received a single dose, the next 8 animals were treated for two consecutive days, and the remaining 8 animals were treated for 4 consecutive days. Prior to dosing, animals were weighed, and the amount administered adjusted according to individual weights.

[0260] Twenty minutes following the first administration of Compound A19, animals from groups 2-5 were intraperitoneally (IP) administered a challenge of a single dose of 5 mg/kg of LPS (from E. coli 0111:B4) at 10 mL/kg. Group 1 served as a control group and received an equivalent volume of water for injection (WFI). Prior to dosing, the animals were weighed and the amount of LPS administered adjusted according to individual weights.

[0261] At pre-determined time-points following administration of the LPS challenge, animals were euthanized, and blood was collected by carotid exsanguination under ketamine

hydrochloride and xylazine anesthesia, followed by separation of serum samples by centrifugation. Brain and liver sampling was also conducted (data not shown). Eight animals from groups 2-5 were sampled at each time-point as follows: 1.5h, 6h, 24h, and 72h, while control animals from group 1 were sampled at 72h post-challenge (20 min-post last dosing) only.

[0262] Blood samples were collected in marked tubes containing protease inhibitors (8:1 v/v; whole blood:protease inhibitors-EDTA free) and left to clot for 30 min. after collection. Following clotting, the samples were centrifuged at 2500×g for 15 min at 21-22 °C, aliquoted as one set of aliquots, snap frozen, and kept at -80°C until cytokine analysis by multiplex was performed. At 72h post-challenge (20 min. post-last dosing), additional 20 µL of serum was separated from groups 3-5, snap frozen, and used for cytokine analysis.

[0263] Cytokines were quantified by multiplex analysis using an Invitrogen Immune Monitoring 48-Plex Mouse ProcartaPlex™ Panel kit according to the manufacturer's instructions and amounts were calculated by interpolation from the standard curve. The panels determine levels of certain cytokines, chemokines, growth factors/regulators and soluble receptors. The panel include pro-inflammatory and anti-inflammatory molecules and other molecules. The cytokines, chemokines, growth factors/regulators and soluble receptors tested were as follows: Cytokines: BAFF, G-CSF (CSF-3), GM-CSF, IFN alpha, IFN gamma, IL-1 alpha, IL-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12p70, IL-13, IL-15/IL-15R, IL-17A (CTLA-8), IL-18, IL-19, IL-22, IL-23, IL-25 (IL-17E), IL-27, IL-28, IL-31, IL-33, LIF, M-CSF, RANKL, and TNF alpha; Chemokines: ENA-78 (CXCL5), Eotaxin (CCL11), GRO alpha (CXCL1), IP-10 (CXCL10), MCP-1 (CCL2), MCP-3 (CCL7), MIP-1 alpha (CCL3), MIP-1 beta (CCL4), MIP-2, and RANTES (CCL5); Growth factors/regulators: Betacellulin (BTC), Leptin, and VEGF-A; and Soluble receptors: IL-2R, IL-7R alpha, IL-33R (ST2).

[0264] As seen in Table 10, at 1.5 hours following LPS administration, mice treated with Compound A19 at 1.5 mg/kg had significantly lower levels of the inflammatory mediators BAFF, G-CSF, ENA-78, Eotaxin, IL-2R, LIF, MIP-1Beta and MIP-1Alpha compared to vehicle-treated LPS animals. Mice treated with Compound A19 at 0.125 mg/kg also exhibited a significant decrease in levels of G-CSF and ENA-78 at this timepoint. At 6 hours post LPS administration, levels of BAFF, ENA-78, and IL-2R remained lowered compared to LPS-treated vehicle mice. In some instances, the LPS challenge resulted in a nominal but not significant increase in levels of inflammatory mediators relative to the group 1 controls, but Compound A19 was able to significantly reduce these levels. These events are denoted by an asterisk in Table 10. These results show that treatment with Compound A19 can mitigate increases in

inflammatory mediators following LPS challenge, suggesting immunomodulatory capabilities of Compound A19.

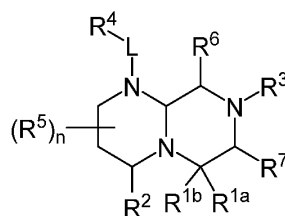
Table 10. Reduction in pro-inflammatory mediator levels

	Timepoint	1.5 hours			6 hours			24 hours			3 days		
	Dose (mg/kg, PO)	0.125	0.5	1.5	0.125	0.5	1.5	0.125	0.5	1.5	0.125	0.5	1.5
Analyte	BAFF			+++			++*						
	G-CSF	+		++									
	ENA-78	++*		++++*			++*						
	Eotaxin			++*									
	IL-2R			++*			++*						
	LIF			+									
	MIP-1Beta			+									
	MIP-1Alpha			+									

+ = p <0.05; ++ = p <0.01; +++ = p <0.001; ++++ = p <0.0001; * = model effect not significant

CLAIMS

1. A method of treating a peripheral and/or systemic inflammatory condition in a subject in need thereof, comprising administering an effective amount of a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof, wherein:

L is a direct bond, $-C(=O)-$, $-(CR^aR^b)_m-C(=O)-$, $-C(=O)-(CR^aR^b)_m-$, or $-(CR^aR^b)_m-$;

each R^a and R^b is independently H, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;

R^{1a} and R^{1b} are independently H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halo, or C₆-C₁₀ arylalkyl;

R^2 is H, oxo, or thioxo;

R^3 is C₂-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₁₂ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₆-C₁₀ arylalkyl, 5- to 10-membered heteroarylalkyl, or 5- to 10-membered heterocyclylalkyl,

wherein the 5- to 10-membered heteroarylalkyl or 5- to 10-membered heterocyclylalkyl contains 1-3 heteroatoms selected from nitrogen and oxygen;

R^4 is C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, or 5- to 10-membered heterocyclyl,

wherein the 5- to 10-membered heteroaryl or 5- to 10-membered heterocyclyl contains 1-3 heteroatoms selected from nitrogen and oxygen;

each R^5 is independently C₁-C₆ alkyl, oxo, or halo;

R^6 is H, C₁-C₆ alkyl, or oxo;

R^7 is H or oxo;

m is 1 or 2; and

n is an integer from 0 to 3;

wherein each C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₂ cycloalkyl,

C₃-C₁₂ cycloalkylalkyl, C₆-C₁₀ aryl, C₆-C₁₀ arylalkyl, 5- to 10-membered heteroaryl, 5- to 10-

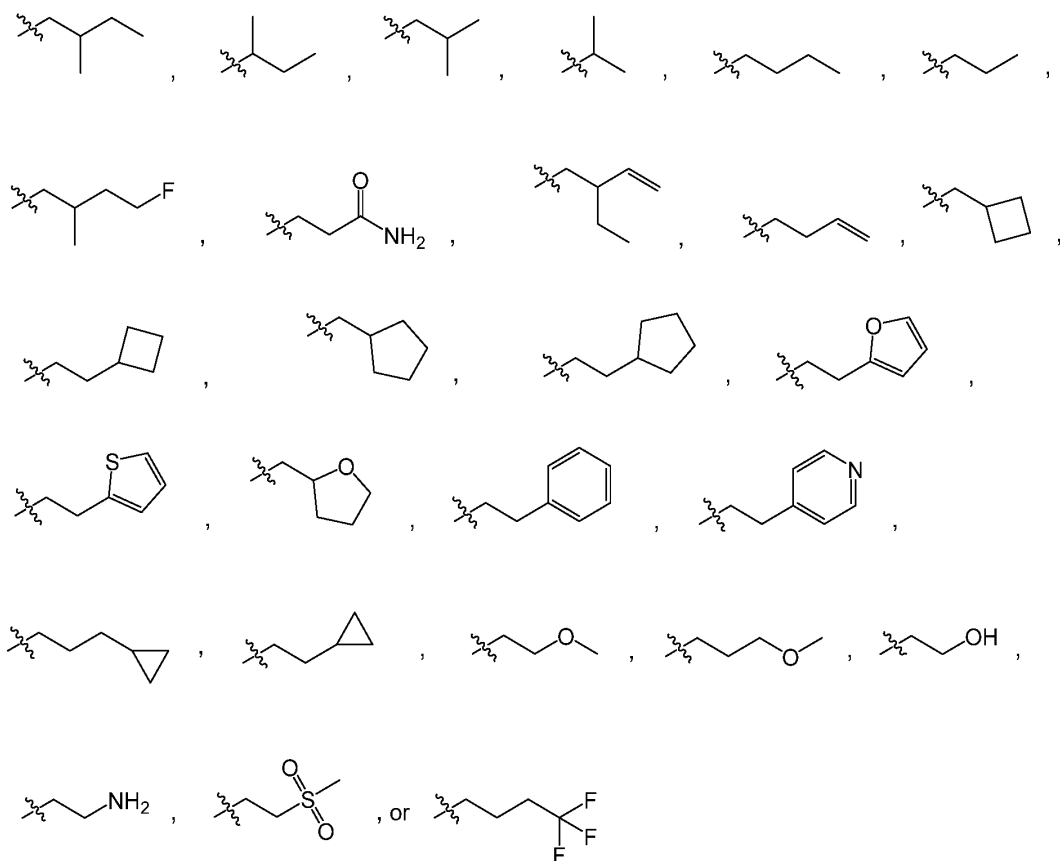
membered heteroarylalkyl, 5- to 10-membered heterocyclyl, and 5- to 10-membered heterocyclalkyl is optionally substituted with one to five substituents selected from hydroxyl, halo, amino, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, cyano, -(C=O)NH₂, nitro, -SO₂(C₁-C₆ alkyl), and -CO₂H.

2. The method of claim 1, wherein L is -C(=O)- or -(CR^aR^b)_m-.
3. The method of claim 1 or 2, wherein L is a -C(=O)-.
4. The method of claim 1 or 2, wherein L is -(CR^aR^b)_m-.
5. The method of claim 4, wherein R^a and R^b are each H, and m is 1.
6. The method of any one of claims 1-5, wherein R^{1a} and R^{1b} are each independently H; C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from halo, -CO₂H, and -C(=O)NH₂; C₁-C₆ alkoxy; halo; or C₆-C₁₀ arylalkyl optionally substituted by 1-3 substituents selected from halo and amino.
7. The method of claim 6, wherein R^{1a} and R^{1b} are each independently H, methyl, fluoro, 2-methylbutyl, -CH₂F, methoxy, -CH₂CO₂H, -CH₂C(=O)NH₂, benzyl, or 4-aminobenzyl.
8. The method of claim 6, wherein R^{1a} and R^{1b} are each independently H or C₁-C₃ alkyl.
9. The method of claim 8, wherein R^{1a} is methyl and R^{1b} is H.
10. The method of claim 8, wherein R^{1a} and R^{1b} are each H.
11. The method of any one of claims 1-10, wherein R² is H.
12. The method of any one of claims 1-10, wherein R² is thioxo.
13. The method of any one of claims 1-10, wherein R² is oxo.
14. The method of any one of claims 1-13, wherein R³ is C₃-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₁₂ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₆-C₁₀ arylalkyl, 5- to 10-membered heteroarylalkyl, or 5- to 10-membered heterocyclalkyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, or heterocyclalkyl is optionally substituted with one to five substituents selected from hydroxyl, halo, amino, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, cyano, -(C=O)NH₂, nitro, -SO₂(C₁-C₆ alkyl), and -CO₂H.

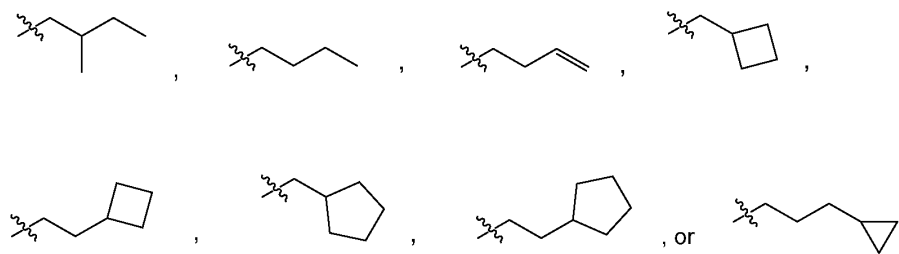
15. The method of any one of claims 1-13, wherein R^3 is C_2 - C_6 alkyl optionally substituted by 1-3 substituents selected from halo, C_1 - C_3 alkoxy, hydroxy, $-NH_2$, $-SO_2(C_1$ - C_3 alkyl), and $-C(=O)NH_2$; C_2 - C_6 alkenyl; C_3 - C_6 cycloalkylalkyl; 5- to 6-membered heteroarylalkyl; 5- to 6-membered heterocyclalkyl; or C_6 arylalkyl.

16. The method of claim 15, wherein R^3 is C_2 alkyl substituted by 1-3 substituents selected from C_1 - C_3 alkoxy, hydroxy, $-NH_2$, and $-SO_2(C_1$ - C_3 alkyl).

17. The method of any one of claims 14-16, wherein R^3 is:



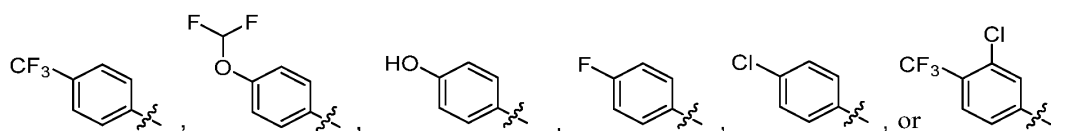
18. The method of claim 17, wherein R^3 is:



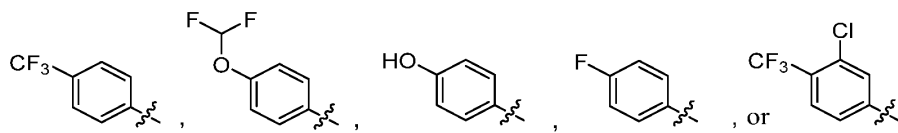
19. The method of any one of claims 1-18, wherein R^4 is C₆-C₁₀ aryl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy.

20. The method of claim 19, wherein R^4 is phenyl substituted with 1-3 substituents selected from -CF₃, -OCHF₂, -OH, fluoro, and chloro.

21. The method of claim 20, wherein R^4 is:



22. The method of claim 21, wherein R^4 is:

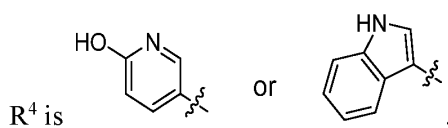


23. The method of any one of claims 1-18, wherein R^4 is 5- to 10-membered heteroaryl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy.

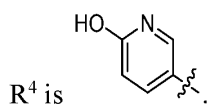
24. The method of claim 23, wherein

R^4 is pyridyl or indolyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy.

25. The method of claim 24, wherein

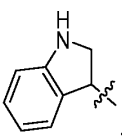


26. The method of claim 25, wherein

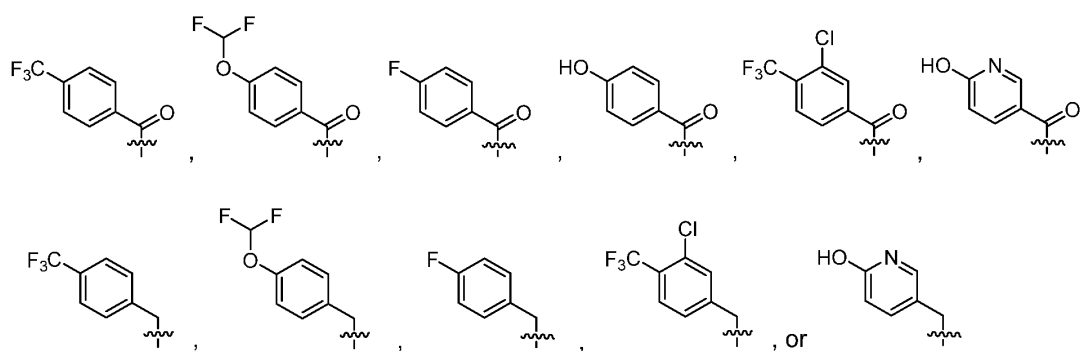


27. The method of any one of claims 1-18, wherein R^4 is 5- to 10-membered heterocyclyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1 - C_6 haloalkyl, and C_1 - C_6 haloalkoxy.

28. The method of claim 27, wherein R^4 is indolinyl.

29. The method of claim 28, wherein R^4 is .

30. The method of any one of claims 1-26, wherein $-L-R^4$ is:



31. The method of any one of claims 1-30, wherein n is 0.

32. The method of any one of claims 1-30, wherein n is 1.

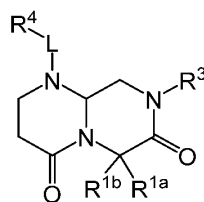
33. The method of claim 32, wherein R^5 is oxo or halo.

34. The method of claim 33, wherein R^5 is oxo or fluoro.

35. The method of any one of claims 1-34, wherein R^6 is H.

36. The method of any one of claims 1-35, wherein R^7 is oxo.

37. The method of any one of claims 1-10, 13-31, 35, and 36, wherein the compound is of Formula (V):



(V), or a pharmaceutically acceptable

salt, isotopic form, or stereoisomer thereof.

38. The method of claim 37, wherein:

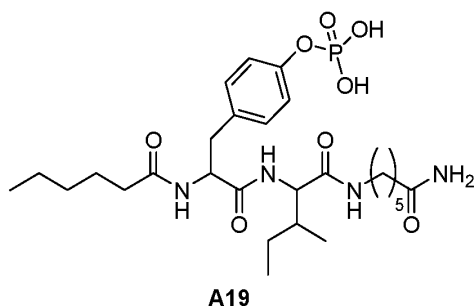
L is -C(=O)- or -CH₂-;

R^{1a} and R^{1b} are independently H or C₁-C₃ alkyl optionally substituted with -CO₂H;

R³ is C₄-C₅ alkyl, C₄-C₅ alkenyl, or C₁-C₃ alkyl substituted with C₃-C₅ cycloalkyl; and

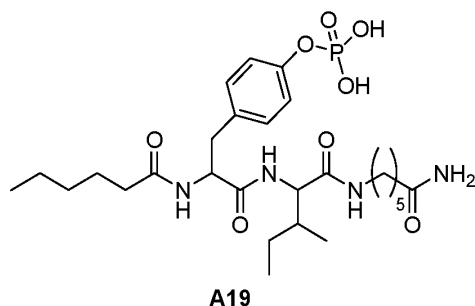
R⁴ is phenyl or pyridyl substituted with 1-3 substituents selected from -CF₃, -OCHF₂, -OH, fluoro, and chloro.

39. A method of treating a peripheral and/or systemic inflammatory condition in a subject in need thereof, comprising administering an effective amount of Compound A19:



or a pharmaceutically acceptable salt, isotopic form, or stereoisomer thereof.

40. A method of treating a peripheral and/or systemic inflammatory condition in a subject in need thereof, comprising administering an effective amount of a compound selected from the compounds of Table 1A and Compound A19:



and pharmaceutically acceptable salts, isotopic forms, or stereoisomers thereof.

41. The method of any one of the preceding claims, wherein the peripheral and/or systemic inflammatory condition is inflammatory bowel disease, Crohn's disease, ulcerative colitis, coeliac disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, dermatomyositis, polymyositis, noninfectious uveitis, optic neuritis, Leber hereditary optic neuropathy (LHON), macular degeneration, retinal degeneration, myasthenia gravis, type 2 diabetes, obesity, coronary heart disease, gout, fatty liver disease, seasonal allergies, chronic obstructive pulmonary disease (COPD), or endometriosis.

42. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is inflammatory bowel disease.

43. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is Crohn's disease.

44. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is ulcerative colitis.

45. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is coeliac disease.

46. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is rheumatoid arthritis.

47. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is psoriasis.

48. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is noninfectious uveitis.

49. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is type 2 diabetes.
50. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is obesity.
51. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is coronary heart disease.
52. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is gout.
53. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is fatty liver disease.
54. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is seasonal allergies.
55. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is COPD.
56. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is endometriosis.
57. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is systemic lupus erythematosus.
58. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is dermatomyositis.
59. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is polymyositis.
60. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is opticus neuritis.
61. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is LHON.

62. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is macular degeneration.
63. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is retinal degeneration.
64. The method of any one of claims 1-41, wherein the peripheral and/or systemic inflammatory condition is myasthenia gravis.
65. The method of any one of the preceding claims, wherein the compound reduces inflammation associated with the inflammatory condition.
66. The method of any one of the preceding claims, wherein the compound reduces hypoxia associated with the inflammation.
67. The method of any one of the preceding claims, wherein the compound reduces pain associated with the inflammatory condition.
68. The method of any one of the preceding claims, wherein the compound decreases the level in the subject of at least one proinflammatory molecule.
69. The method of claim 68, wherein the compound decreases the level of at least one proinflammatory molecule selected from G-CSF, CCL3, CXCL 1, CXCL 2, CXCL10, IL-1 α , IL-1 β , IL-4, IL-10, IL-12p70, IL-17A, TNF- α , and IFN γ .
70. The method of any of one of claims 68 or 69, wherein the compound decreases the level of at least one proinflammatory molecule selected from IL-1 β , IL-4, IL-6, TNF- α , and IFN γ .
71. The method of any one of claims 1-70, wherein the peripheral and/or systemic inflammatory condition is not caused by neuroinflammation or a disease or disorder of the central nervous system.
72. The method of any one of embodiments 1-71, wherein the peripheral and/or systemic inflammatory condition is not caused by Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, traumatic brain injury, or sensorineural hearing and vision loss.

73. The method of any one of embodiments 1-70, wherein the peripheral and/or systemic inflammatory condition is not associated with neuroinflammation or a disease or disorder of the central nervous system.
74. The method of any one of embodiments 1-70, wherein the peripheral and/or systemic inflammatory condition is not associated with Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, traumatic brain injury, or sensorineural hearing and vision loss.
75. The method of any one of embodiments 1-74, wherein the subject is not suffering from Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, traumatic brain injury, sensorineural hearing and vision loss, or a disease or disorder of the central nervous system.
76. The method of any one of the preceding claims, wherein the compound is formulated in a pharmaceutical composition.